Clinical Policy: Sacubitril/Valsartan (Entresto)

Reference Number: CP.PMN.67
Effective Date: 11.01.15
Last Review Date: 08.24
Line of Business: Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Sacubitril/valsartan (Entresto®) is a combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin II receptor blocker (ARB).

FDA Approved Indication(s)

Entresto is indicated:

- To reduce the risk of cardiovascular death and hospitalization for heart failure in 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.
- 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.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Entresto is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Heart Failure (must meet all)**:**

1. Diagnosis of chronic heart failure of NYHA Class II, III, or IV;
2. Prescribed by or in consultation with a cardiologist;
3. Age ≥ 1 year;
4. At the time of request, member has none of the following contraindications:
   a. Concomitant use with ACE inhibitors;
   b. If member has a diagnosis of diabetes, concomitant use with aliskiren;
5. For members with LVEF ≥ 41% (i.e., heart failure with mildly reduced or preserved ejection fraction), failure of dapagliflozin (Farxiga® authorized generic) , unless contraindicated or clinically significant adverse effects are experienced;
6. Dose does not exceed both of the following (a and b):
   a. Sacubitril 194 mg/valsartan 206 mg per day;
   b. 2 tablets for adults per day.

Approval duration: 12 months

B. **Other diagnoses/indications** (must meet 1 or 2)**:**
   1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
      a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.PMN.255 for Medicaid; or
      b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.PMN.16 for Medicaid; or
   2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.PMN.53 for Medicaid.

II. Continued Therapy

A. **Heart Failure** (must meet all)**:**
   1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Entresto for heart failure and has received this medication for at least 30 days;
   2. Member is responding positively to therapy;
   3. If request is for a dose increase, new dose does not exceed both of the following (a and b):
      a. Sacubitril 194 mg/valsartan 206 mg per day;
      b. 2 tablets for adults per day.

   Approval duration: 12 months

B. **Other diagnoses/indications** (must meet 1 or 2)**:**
   1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
      a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.PMN.255 for Medicaid; or
      b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.PMN.16 for Medicaid; or
   2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ACE: angiotensin-converting enzyme
ARB: angiotensin II receptor blocker
FDA: Food and Drug Administration
HFrEF: heart failure with reduced ejection fraction
LVEF: left ventricular ejection fraction
NYHA: New York Heart Association

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
dapagliflozin (Farxiga)	10 mg PO QD	10 mg/day

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Hypersensitivity to any component.
  - History of angioedema related to previous ACE inhibitor or ARB therapy.
  - Concomitant use of Entresto with an ACE inhibitor is contraindicated because of the increased risk of angioedema.
  - Concomitant use of Entresto and ARB should be avoided since Entresto contains an ARB.
  - Concomitant use with aliskiren in patients with diabetes.
- Boxed warning(s): Fetal toxicity; when pregnancy is detected, discontinue Entresto as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

Appendix D: General Information

- The PARAGON-HF trial compared Entresto against valsartan in patients with New York Heart Association class II to IV heart failure, ejection fraction of 45% or higher, elevated level of natriuretic peptides, and structural heart disease for the primary outcome of composite of total hospitalizations for heart failure and death from cardiovascular causes. The results did not find a statistically significantly lower rate of total hospitalizations for heart failure and death from cardiovascular causes among patients with heart failure and an ejection fraction of 45% or higher.
- The 2022 AHA/ACC/HFSA guideline for the management of heart failure defines HFrEF as a clinical diagnosis of heart failure and LVEF ≤ 40%.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Chronic heart failure	Adults The recommended starting dose is 49/51 mg (sacubitril/valsartan) PO BID. Double the dose after 2 to 4 weeks to the target maintenance dose of 97/103 mg (sacubitril/valsartan) BID, as tolerated by the patient. Therapy may be initiated at 24/26 mg (sacubitril/valsartan) PO BID for: • patients not currently taking an ACE inhibitor or an ARB or previously taking a low dose of these agents • patients with severe renal impairment • patients with moderate hepatic impairment Double the dose every 2 to 4 weeks to the target maintenance dose of 97/103 mg (sacubitril/ valsartan) BID, as tolerated by the patient. Pediatric patients age ≥ 1 year Administer weight-based dosing sacubitril/valsartan PO BID. Adjust the dose every 2 weeks, as tolerated by the patient per the following: • Weight < 40 kg*: **Use of oral suspension prepared using the 49/51 mg tablets is recommended. Recommended mg/kg doses are of the combined amount of both sacubitril and valsartan.* o Starting dose: 1.6 mg/kg PO BID o Second titration dose: 2.3 mg/kg PO BID o Third titration dose: 3.1 mg/kg PO BID • Weight ≥ 40 kg and < 50 kg: o Starting dose: 24/26 mg PO BID o Second titration dose: 49/51 mg PO BID o Third titration dose: 72/78 mg PO BID • Weight ≥ 50 kg: o Starting dose: 49/51 mg PO BID o Second titration dose: 72/78 mg PO BID o Third titration dose: 97/103 mg PO BID	Sacubitril 194 mg/valsartan 206 mg per day

VI. Product Availability

- Film-coated tablets (sacubitril/valsartan): 24 mg/26 mg, 49 mg /51 mg, 97 mg/103 mg
- Film-coated oral pellets contained in a hard capsule: 6 mg/6 mg, 15 mg/16 mg

VII. References

1. Entresto Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; April 2024. Available at: https://www.entrestohcp.com. Accessed April 25, 2024.
2. Yancy CW, Jessup M, Bozkurt B, et al. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013;128(16):e240-327.
3. Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2016;134: 000-000.
4. 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: a report of the American College of Cardiology /American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;136:e137-e161.
5. 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. 2021 Feb: 77 (6); 772–810.
6. 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 May, 79 (17) e263–e421. https://doi.org/10.1016/j.jacc.2021.12.012.
7. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993-1004.
8. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med* 2019. 381(17):1609-20. DOI: 10.1056/NEJMoa1908655.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2020 annual review: addition of new FDA labeling for pediatric extension for use in the treatment of symptomatic HF with systemic LV systolic dysfunction; added cardiologist prescriber requirement; revised age restriction from age ≥ 18 years to age ≥ 1 year; added LVEF requirement ≤ 40% for pediatrics per PANORAMA-HF clinical trial; revised quantity limit requirement of 2 tablets per day to apply only to adults since pediatrics may require dosing of up to 3 tablets per day or use of multiple tablets to make sufficient quantity for an oral suspension; references reviewed and updated.	11.26.19	02.20

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2021 annual review: no significant changes; references to HIM.PHAR.21 revised to HIM.PA.154; references reviewed and updated.	10.16.20	02.21
RT4: updated FDA-approved indication for adult patients with chronic heart failure per prescribing information; revised LVEF requirement from less than or equal to 35% to 40% based on updated PI and PARAGON-HF.	03.23.21	05.21
1Q 2022 annual review: no significant changes; references reviewed and updated.	10.18.21	02.22
Per May SDC and prior clinical guidance, added redirection to Jardiance for LVEF ≥ 41%, removed prior requirement restricting use to LVEF ≤ 40%; revised approval durations for Commercial and Medicaid from length of benefit to 12 months.	05.20.22	08.22
Template changes applied to other diagnoses/indications.	10.10.22	
1Q 2023 annual review: no significant changes; references reviewed and updated.	10.27.22	02.23
1Q 2024 annual review: no significant changes; updated contraindications to include concomitant use with aliskiren per PI; references reviewed and updated	11.17.23	02.24
RT4: Added film-coated oral pellets contained in a hard capsule dosage form.	04.25.24	
Per June SDC, split Commercial and HIM line of business into a new policy; revised redirection from Jardiance to dapagliflozin (Farxiga authorized generic).	06.06.24	08.24

Important Reminder
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy,

contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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