# Clinical Policy: Sacubitril/Valsartan (Entresto)

Reference Number: CP.PMN.67
Effective Date: 11.01.15
Last Review Date: 02.21
Line of Business: Commercial, HIM, 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 patients with chronic heart failure (New York Heart Association [NYHA] Class II-IV) and reduced ejection fraction.
  - Entresto is usually administered in conjunction with other heart failure therapies, in place of an angiotensin-converting enzyme (ACE) inhibitor or other ARB.
- 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. Left ventricular ejection fraction (LVEF) is ≤ 35% for adults or ≤ 40% for pediatrics;
5. 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;
6. Dose does not exceed sacubitril 194 mg/valsartan 206 mg (2 tablets for adults) per day.

**Approval duration:**
**HIM** – 12 months
**Commercial/Medicaid** – Length of Benefit

**B. Other diagnoses/indications**

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and 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 sacubitril 194 mg/valsartan 206 mg (2 tablets for adults) per day.

**Approval duration:**
**HIM** – 12 months
**Commercial/Medicaid** – Length of Benefit

**B. Other diagnoses/indications** (must meet 1 or 2)**:**

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   **Approval duration: Duration of request or 12 months (whichever is less)**; or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and 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.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and 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
LVEF: left ventricular ejection fraction
NYHA: New York Heart Association

*Appendix B: Therapeutic Alternatives*

Not applicable

*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.

- 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.

## V. Dosage and Administration

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

| Indication | Dosing Regimen | Maximum Dose |
|---|---|---|
| | ○ Third titration dose: 97/103 mg PO BID | |

## VI. Product Availability

Film-coated tablets (sacubitril/valsartan): 24 mg/26 mg, 49 mg /51 mg, 97 mg/103 mg

## VII. References

1. Entresto Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; October 2019. Available at: https://www.entrestohcp.com. Accessed October 16, 2020.
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. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993-1004.

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| Converted to new template. Added age restriction and contraindications related to DDI per PI/safety approach. Modified max dose requirement to include specific quantity limit. Updated references. | 08.07.17 | 11.17 |
| 1Q18 annual review. Policies combined for Centene Medicaid, Marketplace and Commercial lines of business; No significant change from previous corporate approved policy; Commercial: removed prescriber requirement; added age restriction as safety and effectiveness in pediatric patients have not been established; modified LVEF from < 40% to ≤ 35% per PARADIGM-HF clinical trial; added contraindications related to DDI per PI; updated re-auth to allow COC for heart failure. Added requirement for positive response to therapy; Marketplace and Medicaid: removed prescriber requirement; added age restriction and contraindications related to DDI per PI (Marketplace only); removed "previously tolerated an ACEI or ARB at therapeutic doses for ≥ 30 days" since specialist is involved in care; References reviewed and updated. | 11.01.17 | 02.18 |

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| Medicaid: approval duration changed from 12 months to length of benefit | 03.04.18 | 05.18 |
| 1Q 2019 annual review: no significant changes; references reviewed and updated. | 10.30.18 | 02.19 |
| 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 |
| 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 |

**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.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

**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.