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Last P&T Approval/Version: 01/25/2023
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Policy Number: C8675-A

Entresto (sacubitril/valsartan)

PRODUCTS AFFECTED

Entresto (sacubitril/valsartan)

COVERAGE POLICY

Coverage for services, procedures, medical devices, and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.
This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Chronic heart failure Class II to IV

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review.

A. ADULT CHRONIC HEART FAILURE:
1. (a) Documented diagnosis of chronic heart failure (NYHA Class II, III or IV) AND member has a left ventricular ejection fraction below normal
   OR
   (b) Documented diagnosis of symptomatic heart failure with left ventricular systolic dysfunction
   AND
2. Prescriber attests that member is either: not currently taking another ACE Inhibitor or ARB OR the

member will discontinue the other current ACE Inhibitor or ARB before starting the requested agent
AND

3. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Entresto (sacubitril/valsartan) include: Hypersensitivity to any component, History of angioedema related to previous ACEi or ARB therapy, Concomitant use with ACE inhibitors, Concomitant use with aliskiren in patients with diabetes]
AND
4. FOR WOMEN OF CHILD BEARING POTENTIAL: Prescriber attestation of negative pregnancy testing prior to therapy intiation and have counseled members on risk of harm to fetus should pregnacy occur

B. PEDIATRIC HEART FAILURE:

1. Documentation that Entresto (sacubitril/valsartan) is being used for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction
AND
2. Documentation that the patient has a history of tolerating an angiotensin converting enzyme [ACE] inhibitor, or angiotensin II receptor blocker [ARB]) OR Entresto (sacubitril/valsartan) was initiated during a hospital stay
AND
3. Prescriber attests that member is either: not currently taking another ACE Inhibitor or ARB OR the member will discontinue the other current ACE Inhibitor or ARB before starting the requested agent
AND
4. Documentation of member's current weight (within the last 30 days)
AND
5. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Entresto (sacubitril/valsartan) include: Hypersensitivity to any component, History of angioedema related to previous ACEi or ARB therapy, Concomitant use with ACE inhibitors, Concomitant use with aliskiren in patients with diabetes]
AND
6. The dose of Entresto will not exceed 97/103 mg twice daily

CONTINUATION OF THERAPY:

A. ADULTS: CHRONIC HEART FAILURE:

1. The Entresto dose has been titrated to a dose of 97 mg/103 mg twice daily, or to a maximum dose as tolerated by the patient
AND
2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
AND
3. Documentation of positive clinical response as demonstrated by low disease activity and/or improvements in the condition's signs and symptoms

B. PEDIATRIC HEART FAILURE:

1. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
AND
2. Documentation of positive clinical response as demonstrated by low disease activity and/or improvements in the condition's signs and symptoms
AND
3. Documentation of member's current weight (within the last 30 days)

DURATION OF APPROVAL:
Initial authorization:12 months, Continuation of therapy: 12 months

PRESCRIBER REQUIREMENTS:
Prescribed by or in consultation with a cardiologist

AGE RESTRICTIONS:
1 year of age and older

QUANTITY:
Maximum of 2 tablets per day of any strength

*** An oral suspension may be extemporaneously prepared. The sacubitril: valsartan ratio varies slightly with each tablet strength; only the 49/51 mg tablets can be used to compound the oral suspension to achieve a combined sacubitril and valsartan concentration of 4 mg/mL (sacubitril 1.96mg and valsartan 2.04 mg/mL) ***
Quantity limits may be overridden to allow for compounding in pediatric patients (See Appendix for labeled compounding instructions for reference)
See FDA dosing per label (Appendix)

PLACE OF ADMINISTRATION:
The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
Neprilysin Inhib (ARNI)-Angiotensin II Receptor Antagonist Comb

FDA-APPROVED USES:
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.
- 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.

ENTRESTO is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:

Indication	Titration Step Dose (twice daily)		
	Starting	Second	Final
Adult Heart Failure	49/51 mg	97/103 mg	
Pediatric Heart Failure Patients less than 40 kg	1.6 mg/kg	2.3 mg/kg	3.1 mg/kg
Pediatric Heart Failure Patients at least 40 kg, less than 50 kg	24/26 mg	49/51 mg	72/78 mg
Pediatric Heart Failure Patients at least 50 kg	49/51 mg	72/78 mg	97/103 mg

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Entresto is a combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin II receptor blocker, indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction.

Efficacy

Sacubitril/valsartan was studied in PARADIGM-HF, a multinational, randomized, double-blind trial comparing sacubitril/valsartan 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 ACE inhibitor or ARB for at least four weeks and on maximally tolerated doses of beta-blockers. Patients with a systolic blood pressure of < 100 mmHg at screening were excluded. The primary objective of PARADIGM-HF was to determine whether sacubitril/valsartan, a combination of sacubitril and a RAS inhibitor (valsartan), was superior to a RAS inhibitor (enalapril) alone in reducing the risk of the combined endpoint of cardiovascular (CV) death or hospitalization for heart failure (HF). After discontinuing their existing ACE inhibitor or ARB therapy, patients entered sequential single-blind run-in periods during which they received enalapril 10 mg twice-daily, followed by sacubitril/valsartan 100 mg twice-daily, increasing to 200 mg twice daily. Patients who successfully completed the sequential running periods were randomized to receive either sacubitril/valsartan 200 mg (N=4,209) twice-daily or enalapril 10 mg (N=4,233) twice-daily. The primary endpoint was the first event in the composite of CV death or hospitalization for HF. The median follow-up duration was 27 months and patients were treated for up to 4.3 years. The mean left ventricular ejection fraction was 29%. The underlying cause of heart failure was coronary artery disease in 60% of patients; 71% had a history of hypertension, 43% had a history of myocardial infarction, 37% had an eGFR < 60 mL/min/1.73m2, and 35% had diabetes mellitus. Most patients were taking betablockers (94%), mineralocorticoid antagonists (58%), and diuretics (82%). Few patients had an implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy defibrillator (CRT-D) (15%). PARADIGM-HF demonstrated that sacubitril/valsartan, was superior to enalapril, in reducing the risk of the combined endpoint of cardiovascular death or hospitalization for heart failure, based on a time-to-event analysis (hazard ratio [HR]: 0.80, 95% confidence interval [CI], 0.73, 0.87, p=0.0001). The treatment effect reflected a reduction in both cardiovascular death and heart failure hospitalization. Sudden death accounted for 45% of cardiovascular deaths, followed by pump failure, which accounted for 26%. Sacubitril/valsartan also improved overall survival (HR 0.84; 95% CI [0.76, 0.93], p = 0.0009). This finding was driven entirely by a lower incidence of cardiovascular mortality on sacubitril/valsartan.

Safety

During the sacubitril/valsartan run-in period, an additional 10.4% of patients permanently discontinued treatment, 5.9% because of an adverse event, most commonly renal dysfunction (1.8%), hypotension (1.7%) and hyperkalemia (1.3%). Because of this run-in design, the adverse reaction rates described below are lower than expected in practice. In the double-blind period, safety was evaluated in 4,203 patients treated with sacubitril/valsartan and 4,229 treated with enalapril. In

PARADIGM-HF, patients randomized to sacubitril/valsartan received treatment for up to 4.3 years, with a median duration of exposure of 24 months; 3,271 patients were treated for more than one year. Discontinuation of therapy because of an adverse event during the double-blind period occurred in 450 (10.7%) of sacubitril/valsartan treated patients and 516 (12.2%) of patients receiving enalapril. Adverse reactions occurring at an incidence of ≥5% in patients who were treated with sacubitril/valsartan in the double-blind period are shown below: In the PARADIGM-HF trial, the incidence of angioedema was 0.1% in both the enalapril and sacubitril/valsartan run-in periods. In the double-blind period, the incidence of angioedema was higher in patients treated with sacubitril/valsartan than enalapril (0.5% and 0.2%, respectively). The incidence of angioedema in Black patients was 2.4% with sacubitril/valsartan and 0.5% with enalapril. Orthostasis was reported in 2.1% of patients treated with sacubitril/valsartan compared to 1.1% of patients treated with enalapril during the double-blind period of PARADIGM-HF. Falls were reported in 1.9% of patients treated with sacubitril/valsartan compared to 1.3% of patients treated with enalapril. Sacubitril/valsartan carries a black box warning that drugs that act directly on the renin angiotensin system can cause injury and death to the developing fetus and when pregnancy is detected, sacubitril/valsartan should be discontinued as soon as possible.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Entresto (sacubitril/valsartan) are considered experimental/investigational and therefore, will follow Molina's Off-Label policy. Contraindications to Entresto (sacubitril/valsartan) include: Hypersensitivity to any component, History of angioedema related to previous ACEi or ARB therapy, Concomitant use with ACE inhibitors, Concomitant use with aliskiren in patients with diabetes.

OTHER SPECIAL CONSIDERATIONS:
None

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Entresto tablets 24-26MG
Entresto tablets 49-51MG
Entresto tablets 97-103MG

REFERENCES

1. Entresto (sacubitril/valsartan) [prescribing information]. Novartis Pharmaceuticals Corporation. East Hanover, NJ. February 2021.
2. McMurray JJ, Desai AS, Gong J. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial (PARADIGM-HF). European Journal of Heart Failure 2013; 15: 1062–1073

3. McMurray JJ, Packer M, Desai AS, et al. Angio-tensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993-1004.
4. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure. Circulation 2013; 128:e240-e327.
5. Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFS A Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure. Circulation. 2016; 134:e282-e293.
6. Shaddy R, Canter C, Halnon N, et al. Design for the sacubitril/valsartan (LCZ696) compared with enalapril study of pediatric patients with heart failure due to systemic left ventricle systolic dysfunction (PANORAMA-HF study). Am Heart J. 2017;193:23-34.

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Quantity Contraindications/Exclusions/Discontinuation	Q1 2023
Q2 2022 Established tracking in new format	Historical changes on file