BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE:	**1/21/16**
LAST REVIEW DATE:	**8/15/19**
LAST CRITERIA REVISION DATE:	**8/15/19**
ARCHIVE DATE:	

ENTRESTO™ (sacubitril and valsartan) oral tablet

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy 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 BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

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Criteria:

- **Criteria for initial therapy:** Entresto (sacubitril and valsartan) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in Cardiology or in consultation with a Cardiologist
  2. Individual is 18 years of age or older
  3. A confirmed diagnosis of symptomatic chronic heart failure, New York Heart Association Class II-IV
  4. Left ventricular ejection fraction is ≤ 40%
  5. Individual has been on a stable dose of ACE inhibitor or ARB therapy for at least 4 weeks
  6. Most recent (while on therapeutic or maximally tolerated doses of evidence-based medications for heart failure) B-type natriuretic peptide level (BNP) or N-terminal pro-BNP level is **EITHER**:
     - ≥ 150 pg/mL (or NT-proBNP ≥ 600 pg/mL)
     - ≥ 100 pg/mL (or NT-proBNP ≥ 400 pg/mL) if hospitalized for heart failure in the last 12 months
  7. ACE inhibitor or other ARB will be discontinued before starting Entresto, with ACE inhibitor discontinued at least 36 hours before start of Entresto
  8. Will be used in conjunction with an evidence based beta-blocker at maximally tolerated dose and other therapies for heart failure such as aldosterone antagonist in selected individuals
  9. There are no contraindications
     - Contraindications include:
       - History of angioedema to previous ACE inhibitor therapy
       - History of angioedema to previous ARB therapy
       - Simultaneous use with ACE inhibitor therapy
       - Use within 36 hours of an ACE inhibitor therapy
       - Simultaneous use with aliskiren in patients with diabetes
       - Hypersensitivity to any component

  Initial approval duration:

  - If the individual has **NOT** been seen by a cardiologist within 6 months **AND** the request is for initial **OR** continuation of therapy: 60-day transition of care period to permit ample time to be seen by a cardiologist
  - If seen by a cardiologist: 12 months

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- **Criteria for continuation of coverage (renewal request):** Entresto is considered ***medically necessary*** and will be approved with documentation of **ALL** of the following:

  1. Individual continues to be seen by a physician specializing in Cardiology or is in consultation with a Cardiologist at least yearly

  2. There are no hospitalizations for heart failure in the last 12 months while on therapy

  3. Individual has been adherent with the medication

  4. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use, such as:
     - As listed in the Criteria Initial therapy section above
     - Angioedema
     - Untreated hyperkalemia
     - Progressive and/or significant deterioration of kidney function

  5. There are no significant interacting drugs

  Renewal duration: 12 months

Description:

Ernesto (sacubitril and valsartan) is a combination of the neprilysin inhibitor, sacubitril, and the angiotensin II receptor blocker (ARB), valsartan. It 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 (sacubitril and valsartan) is administered in conjunction with other heart failure therapies in place of angiotensin converting enzyme (ACE) inhibitors and other ARB.

Sacubitril is a prodrug that is converted to its active metabolite which inhibits neutral endopeptidase (neprilysin). Valsartan inhibits the effects of angiotensin II by selectively blocking at the angiotensin (AT)-1 receptor and it inhibits angiotensin II-dependent aldosterone release.

Heart failure (HF) is a complex chronic progressive clinical syndrome in which the heart muscle is unable to pump enough blood to meet the body's needs. Diagnosis is made based on a careful history and physical examination. Mortality rate is high, approximately 50% of patients die within five years of diagnosis despite the availability of medications with proven mortality benefit.

NYHA categorizes HF into four classes depending on a patient's functional status, ranging from no limitation in physical activity (Class I), to an inability to carry out any physical activity without discomfort (Class IV). Treatment options for NYHA class II to IV heart failure with reduced ejection fraction include ACE inhibitors or ARB, angiotensin receptor neprilysin inhibitors (ARNIs), beta-blockers (bisoprolol, carvedilol, or sustained release metoprolol), and

aldosterone antagonists (eplerenone or spironolactone). Loop diuretics and vasodilators (hydralazine with isosorbide dinitrate) are added depending on symptoms and ethnicity. Digoxin may also be used in certain circumstances.

According to current guidelines, beta-blockers and ACE inhibitors, ARBs, or ARNIs are the cornerstone of the management of HF, and have been shown in randomized controlled studies to reduce HF associated morbidity and mortality. Entresto (sacubitril and valsartan) has not been evaluated for monotherapy for heart failure with reduced ejection fraction, for the treatment of heart failure with preserved ejection fraction, or in the treatment of hypertension.

Signs and symptoms of HF are a result of compensatory mechanisms involved in an effort to restore cardiac output. Neurohumoral adaptations include activation of the renin-angiotensin-aldosterone (RAAS) and the sympathetic adrenergic nervous system, increased release of vasopressin (antidiuretic hormone) and various natriuretic peptides. The net effect of the neurohumoral response is to cause vasoconstriction and to increase blood volume. Over time these compensatory change can worsen heart failure. Prolonged HF also leads to a depletion of several endogenous vasoactive peptides are involved in vasodilation, natriuresis, diuresis, and inhibition of pathologic growth and fibrosis.

Vasoactive peptides include atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP), bradykinin, adrenomedullin, substance-P, vasoactive intestinal peptide, and calcitonin gene regulated peptide. Release into the circulation is stimulated by sodium overload, increase in extracellular volume, distension of auricles and ventricles. Their plasma half-life is very short as they are inactivated by neprilysin which degrades these to inactive products. Neprilysin expression is upregulated in heart failure patients. Inhibition of neprilysin increases the levels of vasoactive peptides, countering the neurohurmoral overactivation that contributes to vasoconstriction, sodium retention, and maladaptive remodeling.

Assays for BNP (B-type natriuretic peptide) and NTproBNP (N-terminal pro-B-type natriuretic peptide), are both natriuretic peptide biomarkers, have been used increasingly to establish the presence and severity of heart failure. A substantial evidence base exists that supports the use of natriuretic peptide biomarkers to assist in the diagnosis or exclusion of heart failure as a cause of symptoms. Current clinical practice guidelines give a Class I recommendation to measure BNP or NT-proBNP to support a clinical diagnosis of heart failure, to assess disease severity, or to establish prognosis.

Angiotensin II that interacts with its AT-1 receptor causes vasoconstriction, sodium and water retention, and fibrosis/hypertrophy. Use of an ARB prevents these actions of angiotensin II.

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Definitions:

New York Heart Association (NYHA) Classification:

Class I	No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc
Class II	Mild symptoms mild dyspnea and/or angina, fatigue, palpitations, and slight limitation during ordinary activity or moderate exercising but not during rest
Class III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20-100 m) or minimal exertion that interfere with normal daily activity, comfortable only at rest
Class IV	Severe limitations, unable to carry out any physical activity because experiences symptoms even while at rest that worsen with any exertion, mostly bedbound patients

Resources:

Entresto. Package Insert. Revised by manufacturer 07/2015. Accessed 07-23-2015.

Entresto. Package Insert. Revised by manufacturer 08/2015. Accessed 08-24-2017.

Entresto. Package Insert. Revised by manufacturer 11/2017. Accessed 07-19-2018.

McMurray JJ, Packer M, Desai AS, et al.: Angiotensin-Neprilysin inhibitors verses Enalapril in Heart Failure. NELM 2014 Sep 11; 371(11): 993-1004.

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. JACC 2016; doi: 10.1016/j.jacc.2016.05.011.

UpToDate: Pharmacologic therapy of heart failure with reduced ejection fraction. Current through Jul 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/pharmacologic-therapy-of-heart-failure-with-reduced-ejection-fraction?source=search_result&search=heart%20failure%20treatment&selectedTitle=2~150#H17678370