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New Drug Evaluation: sacubitril/valsartan tablet, oral

Date of Review: September 2015
Generic Name: sacubitril/valsartan
PDL Class: not applicable

End Date of Literature Search: July 1, 2015
Brand Name (Manufacturer): Entresto™ (Novartis)
Dossier Received: yes

Research Questions:

1. What is the evidence for sacubitril/valsartan to reduce mortality and cardiovascular (CV) morbidities; and if available, how does the drug's efficacy compare to ACE-inhibitors (ACE-I) and angiotensin II receptor blockers (ARB) when used to manage chronic heart failure with reduced ejection fraction (HFrEF)?
2. Based on the evidence available, does sacubitril/valsartan have a clear place in therapy for chronic HFrEF compared to ACE-Is and ARBs?
3. How well is sacubitril/valsartan tolerated in patients; and if available, how does the safety of sacubitril/valsartan compare to ACE-Is and ARBs when used to manage chronic HFrEF?
4. Are there subgroups of patients in which sacubitril/valsartan may be safer or more effective than ACE-Is or ARBs when used to manage chronic HFrEF?

Conclusions:

- Evidence for use of sacubitril/valsartan is limited to one 27-month clinical trial (n=8,399) with low and moderate risk of selection and performance bias, respectively.[1] The study was composed of patients with stable, mildly symptomatic HFrEF (New York Heart Association [NYHA] Classes II and III) with a mean ejection fraction (EF) of 29%. Patients in the study remained on standard HF therapy (ie, beta-blocker, diuretic(s), aldosterone antagonist).[1]
- There is low to moderate quality evidence that sacubitril/valsartan 97/103 mg twice daily (BID) can reduce risk of death from CV causes or hospitalization for HF by an absolute difference of 4.7% compared to enalapril 10 mg BID (21.8% vs. 26.5%, respectively; Hazard Ratio [HR]=0.80 (95% Confidence Interval [CI] 0.73-0.87; p<0.001; number needed-to-treat [NNT] 22).[1]
- There is low quality evidence, based on a secondary endpoint, that sacubitril/valsartan may reduce all-cause mortality, driven almost entirely by reduction in CV mortality, by an absolute difference of 2.8% compared to enalapril (17.0% vs. 19.8%, respectively; HR=0.84 (95% CI, 0.76-0.93; p<0.001; NNT 36).[1]
- There is low quality evidence that sacubitril/valsartan may not reduce perceived quality of life and health status versus enalapril when assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ).[1] The difference in KCCQ scores were statistically significant when assessed at 8 months (a difference of 1.61 points on a 100-point scale),[1] but a much larger difference is needed to be clinically meaningful.[2,3]
- There is insufficient evidence to determine if the results seen were driven by the maximum daily dose of valsartan (320 mg) or by the addition of the neprilysin inhibitor sacubitril to maximally dosed valsartan. Additional studies will help guide place in therapy for sacubitril/valsartan in the management of HFrEF, including whether a neprilysin inhibitor with an ARB will replace an ACE-I or ARB in most HFrEF patients.

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- Safety data are limited to the one trial. There is low quality evidence that sacubitril/valsartan may be tolerated similarly as enalapril, but sacubitril/valsartan was associated with more episodes of symptomatic hypotension than enalapril (14.0% vs. 9.2%, respectively).[1] Enalapril was associated higher incidence of cough than sacubitril/valsartan (14.3% vs. 11.3%, respectively) and higher incidence of hyperkalemia >6.0 mEq/L (5.6% vs. 4.3%, respectively).[1]
- Based on study methodology, there is insufficient evidence of a dose-response for sacubitril/valsartan, and a daily dose of 400 mg is needed to expect the mortality and morbidity benefits demonstrated in the trial.
- Based on the population studied, there is insufficient evidence for the use of sacubitril/valsartan in the following populations: NYHA class I or IV, HF patients with preserved EF, pediatric populations, very elderly populations, patients with refractory hypertension or marginally low blood pressure, or ACE-I-naïve patients.[1] Blacks were also underrepresented in this trial despite the high prevalence of HF and higher incidence of angioedema in this population.[4]

Recommendation:

- Restrict use of sacubitril/valsartan to populations where it has demonstrated efficacy. See **Appendix 2** for the proposed prior authorization criteria.

Background:

Cardiac remodeling observed in both infarcted and non-infarcted myocardium is recognized as a major factor in the development of impaired LV dysfunction and HFrEF.[5] Cardiac remodeling involves molecular and cellular changes to the cardiomyocytes and interstitium which results structural and functional modification of the heart.[5] Cardiac dilatation, interstitial fibrosis, and reduction in contractility and relaxation are all consequences of cardiac remodeling.[5] The goals of management of HFrEF (ie, systolic HF) are to prevent hospital admission and improve survival, and to relieve signs (eg, edema) and symptoms (eg, dyspnea).[6] The cornerstone of drug therapy in chronic HFrEF is inhibition of the neurohormonal activation present in HFrEF that promotes cardiac remodeling.[6,7] The most well-studied system in the renin-angiotensin-aldosterone system (RAAS), and inhibition of RAAS has shown to have a significant impact on the pathophysiology and progression of HF.[6,7] Drugs that inhibit neurohormonal activation in HFrEF have consistently proven to reduce all-cause mortality in chronic HFrEF patients (NYHA class I-IV).[6,7] These drugs include an ACE-I (alternatively, an ARB if an ACE-I is not tolerated), a select beta-blocker (bisoprolol, carvedilol, or sustained-release metoprolol succinate), and for most patients, a mineralcorticoid (aldosterone) receptor antagonist (spironoloactone or eplerenone).[6,7] Both an ACE-I and a beta-blocker should be initiated as soon as HFrEF is diagnosed.[6,7]

An ACE-I can reduce mortality and hospitalizations, improve symptoms, exercise tolerance and performance, and improve quality of life in patients with HFrEF.[6,7] The benefits of ACE inhibition are seen in patients with mild, moderate or severe symptoms of HF and in patients with or without CAD.[7] The addition of a beta-blocker to an ACE-I further improves morbidity outcomes and mortality in these patients.[6] Long-term treatment with the aforementioned beta-blockers also improve symptoms of HF, improve functional status, and enhance the patient's overall sense of well-being.[6,7] However, these benefits should not be considered a class effect. Other beta-blockers, including metoprolol tartrate, were less effective in HF trials.[7] Nebivolol demonstrated a modest but non-significant reduction in the primary endpoint of all-cause mortality or CV hospitalization but did not affect mortality alone in an elderly population with both reduced and preserved EF.[8] Aldosterone antagonists are recommended to reduce morbidity and mortality in patients with NYHA class III-IV who have reduced EF (≤35%), though their benefits probably extend to all patients with HFrEF.[6,7] Patients with NYHA class II with reduced EF also benefit from an aldosterone antagonist if they have a history of previous CV hospitalization or have elevated plasma natriuretic peptide levels.[7] However, renal function and potassium should be routinely monitored because of risk for hyperkalemia in susceptible patients, such as those with renal insufficiency.

In most controlled clinical trials that were designed to evaluate mortality, the dose of the ACE-I/ARB, beta-blocker and aldosterone antagonist was not determined by the patient's therapeutic response but was increased until the predetermined target dose was reached. Current guidelines recommend clinicians use every effort to reach the study doses achieved in clinical trials that have demonstrated efficacy to reduce CV events (see Table 1).[6,7]

Table 1. Drugs Shown to Improve Mortality/Morbidity in Chronic Heart Failure with Reduced Ejection Fraction. Adapted from 2012 ESC Guidelines.[6]

ACE Inhibitors	Angiotensin-2 Receptor Blockers	Beta-Blockers	Aldosterone Antagonists
• Captopril 50 mg TID* • Enalapril 10-20 mg BID • Lisinopril 20-35 mg QDay^ • Ramipril 5 mg BID • Trandolapril 4 mg QDay*	• Candesartan 32 mg QDay • Losartan 150 mg QDay^ • Valsartan 160 mg BID	• Bisoprolol 10 mg Qday • Carvedilol 25-50 mg BID • Metoprolol succinate (XL/ER) 200 mg QDay	• Eplerenone 50 mg QDay • Spironolactone 25-50 mg QDay

Abbreviations: BID = twice daily; QDay = once daily; TID = three times daily; XL/ER = extended-release formulation
* Indicates an ACE inhibitor where the dosing target is derived from post-myocardial infarction trials.
^ Indicates drugs where a higher dose has been shown to reduce morbidity/mortality compared with a lower dose of the same drug, but there is no substantive placebo-controlled randomized controlled trial and the optimum dose is uncertain.

There are also other therapeutic options for management of HFrEF that do not inhibit RAAS or other components of neurohormonal activation. Hydralazine and isosorbide dinitrate has shown to decrease morbidity and mortality in self-identified African-Americans/Blacks with NYHA class III-IV and reduced EF.[7] Digoxin has no effect on survival, but it can have a modest effect on reducing hospitalizations regardless of the underlying rhythm or cause of HF (ischemic or non-ischemic cardiomyopathy).[7] In Europe, consideration for ivabradine (approved by European Medicines Agency in 2005 and U.S. Food and Drug Administration in 2015) is given to reduce HF hospitalization in patients in sinus rhythm with an EF of 35% or less, a HR of at least 70 beats-per-minute, and persistent symptoms (NYHA class II-IV) despite a recommended dose of a beta-blocker, an ACE-I/ARB and an aldosterone antagonist.[6]

Neprilysin inhibitors were first investigated as a therapeutic strategy in HF in the 1990s.[5] Neprilysin is a neutral endopeptidase that degrades vasoactive peptides such as natriuretic peptides and bradykinin.[1] Natriuretic peptides, which include atrial natriuretic peptide and B-type natriuretic peptide, are secreted by the heart in response to increased cardiac wall stress (it is also secreted by other organs in response to other stimuli).[9] Natriuretic peptides have potent natriuretic properties, also inhibits RAAS, and reduces sympathetic drive.[9] Inhibiting neprilysin increases the levels of these peptides and counters the neurohormonal activation associated with vasoconstriction, sodium retention and cardiac remodeling.[1] However, the combined use of an ACE-I and a neprilysin inhibitor (enalapril/omapatrilat) was associated with serious angioedema when studied in HF.[10] Subsequently, sacubitril, a prodrug converted into the neprilysin inhibitor LBQ657, was studied in combination with an ARB (valsartan) in patients with HFrEF in the PARADIGM-HF trial.[1] Evidence from this trial was used by the U.S. Food and Drug Administration (FDA) to grant approval for its use in July 2015.[11] The combination of sacubitril and valsartan (previously referred to as LCZ696) is indicated to reduce the risk of cardiovascular death and hospitalization for HF in patients with chronic NYHA class II-IV HF with reduced EF.[12] Sacubitril/valsartan is a first-in-class angiotensin receptor neprilysin inhibitor (ARNI). After ingestion, the drug delivers systemic exposure of sacubitril, a neprilysin inhibitor pro-drug, and valsartan.[12] Sacubitril is rapidly metabolized by esterases to the active neprilysin inhibitor LBQ657.[12] The twice daily maintenance dose of the sacubitril/valsartan 97/103 mg formulation yields plasma concentrations of valsartan equivalent to valsartan 160 mg twice daily.[13]

In HF patients with preserved EF (HFpEF), sacubitril/valsartan was compared to valsartan in a phase 2 trial evaluating reduction in N-terminal pro-brain natriuretic peptide (NT-proBNP) from baseline.[14] There was a superior reduction of NT-proBNP with sacubitril/valsartan compared to valsartan alone at 12 weeks; however, this difference in reduction was lost by 36 weeks.[14] Research is currently underway to determine how sacubitril/valsartan compares to valsartan alone when clinically relevant outcomes are assessed in patients with HFpEF (NCT01920711).[15] Other future therapeutic considerations may also include refractory hypertension – sacubitril/valsartan significantly improved systolic blood pressure (SBP) by -6.01 mmHg compared to valsartan 320 mg daily.[16]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including the Black Boxed Warning on fetal toxicity associated with drugs that act directly on the RAAS, indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

The 'Prospective comparison of Angiotensin Receptor neprilysin inhibitors with Angiotensin converting enzyme inhibitors to Determine Impact on Global Mortality and morbidity in Heart Failure' (PARADIGM-HF, NCT01035255) trial was a randomized, double-blind, active-controlled, multi-centered trial that compared the long-term efficacy and safety of sacubitril/valsartan with enalapril in patients with chronic HFrEF (EF ≤35%). Table 4 provides details of the study methodology, results, biases, and applicability. The investigators used an innovative approach: instead of adding new therapy to standard of care, the investigators substituted a cornerstone of HF therapy, the ACE-I, for sacubitril/valsartan. The investigators used a careful, step-wise approach to their study to maximize safety. First, there was a screening period to assess patient eligibility based on multiple inclusion and exclusion criteria. The screening period was followed by a single-blind run-in period to determine if the eligible patients (n=10,521) were able to tolerate a target dose of enalapril 10 mg BID, which was followed by a 36-hour washout period and a second single-blind run-in period to determine if patients who tolerated the target dose of enalapril could also tolerate the target dose of sacubitril/valsartan 200 mg BID. Over 20% of eligible patients based on the inclusion and exclusion criteria were not eligible for randomization into the clinical trial – mostly because of intolerance to the target doses. Patients who could tolerate target doses of both drugs were randomized 1:1 to enalapril 10 mg BID (n=4,212) or sacubitril/valsartan 200 mg BID (n=4,187) for the clinical trial.

Baseline characteristics were similar between the groups. Overall, the population studied had stable, mildly symptomatic HFrEF on recommended HF therapy. Only about 5% of patients enrolled at sites in the United States.[17] Most patients were white males, with few females or racial and/or ethnic groups represented other than moderately sized number of Asian populations represented. The mean EF was 29% and most patients had NYHA class II HF, and about one-quarter had NYHA class III HF. Most patients concurrently received beta-blockers and diuretics. The median duration of follow-up was 27 months. Interestingly, the SBP was relatively equal between groups and baseline (121-122 mmHg) but mean SBP at 8 months was 3.2±0.4 mmHg lower in the sacubitril/valsartan group than in the enalapril group ($p<0.001$).

The primary end point included a composite of death from cardiovascular causes or first hospitalization for HF. Key secondary endpoints included all-cause mortality, change in the clinical summary score on the KCCQ, time to new onset atrial fibrillation, and time to the first decline in renal function. The KCCQ is a validated 23-item, self-administered instrument that quantifies physical function, symptoms, social function, and quality of life.[2,3,18] An overall summary score is derived and Scores are transformed to a range of 0-100, in which higher scores reflect better health status.[2,18]

Prior to the scheduled completion of the study, the trial was terminated early based on meeting the pre-specified boundary of overwhelming benefit for the primary end point (enalapril, 26.5% vs. sacubitril/valsartan, 21.8%; HR=0.80 (95% CI, 0.73-0.87; $p<0.001$). The absolute difference of 4.7% predicts that 22 patients would need to be treated for 27 months with sacubitril/valsartan instead of enalapril to prevent one hospitalization for HF or one death from CV causes. The effect of sacubitril/valsartan was fairly consistent across multiple subgroups except for those without prior use of an ACE-I, in which the effect of sacubitril/valsartan was unclear.

All-cause mortality was also significantly reduced with sacubitril/valsartan compared to enalapril (17.0% vs. 19.8%, respectively; HR=0.84 (95% CI, 0.76-0.93; $p<0.001$). The absolute difference of 2.8% demonstrates that 36 patients would need to be treated with sacubitril/valsartan for 27 months instead of enalapril to prevent one death. KCCQ scores improved by 1.61 points (scale, 0-100) with sacubitril/valsartan compared to enalapril. However, a variation of up to 4 points is frequently observed in stable HF patients[2] and a minimal 10-point improvement in the KCCQ is required to have important prognostic significance.[3] Thus, it is

doubtful patients in the PARADIGM-HF trial perceived better quality of life and health-status on sacubitril/valsartan compared to those on enalapril, but the difference was nonetheless statistically significant (p=0.001). The incidence of new-onset atrial fibrillation and protocol-defined decline in renal function (see evidence table) were similar between the 2 treatment groups.

Follow-up analyses of PARADIGM-HF trial data show patients who received sacubitril/valsartan also had slower deterioration of their clinical condition compared to those who received enalapril, which was evidenced by less intensification of drug therapy, emergency department visits and hospitalizations, and less use of advanced treatment modalities, such as inotropes, left ventricular assist devices or heart transplantation.[19]

The study had several strengths, such as its size, duration of follow-up, and the compelling effect sizes in the results. However, several limitations should also be noted. First, the order of the single-blinded run-in phases can compromise both internal validity and applicability of the study. Bias is introduced with the familiarization of treatment effect, especially in patients previously on an ACE-I. Alternatively, investigators un-blinded during the initial phases of the study may become familiar with how a patient responded to both treatments. If this occurs, blinding is compromised after randomization and treatment allocation. About 20% in each study arm still dropped out of the study prematurely, which can significantly impact the applicability of the study after consideration for the 20% of eligible patients who were not randomized into the trial because of intolerance to the drugs in the run-in phases. Second, it is not clear if the efficacy of sacubitril/valsartan can be attributed to the addition of the neprilysin inhibitor to a maximally dosed valsartan, or if it can be attributed to the maximally dosed valsartan alone. Both doses of valsartan and enalapril in this study are optimal,[20–22] but a comparison of sacubitril/valsartan to valsartan 320 mg daily would be helpful to explain the benefits of the neprilyxin inhibitor when added to valsartan. An ACE-I is preferred to an ARB for management of HF based on superior mortality data; however, when valsartan has been directly compared to enalapril in different populations, various outcomes studied show that a daily 40 mg dose of enalapril may have been a more reasonable comparator.[23–26] Third, the study was spread out among 1043 sites in 47 countries.[1] With so many participating sites, there would have been an average of 8 patients enrolled at each site, which may have affected the ability to monitor quality and recognize discrepancies. Lastly, early termination of randomized controlled trials tend to exaggerate differences between comparator groups,[27] though the difference between the arms in the primary endpoint appeared to be consistent throughout the 27-month trial.[1]

Clinical Safety:
Overall, sacubitril/valsartan and enalapril were tolerated equally well and no major or unanticipated safety issues were identified in this Phase 3 trial.[1] The study drug was discontinued in 19.8% of patients on enalapril and 17.8% on sacubitril/valsartan.[1] Fewer patients who received sacubitril/valsartan discontinued their treatment because of an adverse event when compared to those who received enalapril (10.7% vs. 12.3%, respectively; p=0.03).[1] There were more patients who experienced angioedema with sacubitril/valsartan than with enalapril, but these events were relatively low overall (0.45% vs. 0.24%, respectively).[1] Symptomatic hypotension also occurred more frequently with sacubitril/valsartan (14.0% vs. 9.2%; p<0.001).[1] However, elevated serum creatinine ≥2.5 mg/dL (4.5% vs. 3.3%; p=0.007), elevated serum potassium >6.0 mEq/L (5.6% vs. 4.3%; p=0.007), and cough (14.3% vs. 11.3%; p<0.001) occurred more frequently with enalapril.[1] The common adverse reactions reported in the PARADIGM-HF trial are noted in Table 2.

Table 2. Adverse Reactions Reported in ≥5% of Patients Treated with Sacubitril/Valsartan in PARADIGM-HF.[12]

	Sacubitril/Valsartan (n=4,203)	Enalapril (n=4,229)
Hypotension	18%	12%
Hyperkalemia	12%	14%
Cough	9%	13%
Dizziness	6%	5%
Renal Failure/Acute Renal Failure	5%	5%

Patients on sacubitril/valsartan should be regularly monitored initially to assess for deteriorating renal function, hypotension and hyperkalemia. At a minimum, patients enrolled in the PARADIGM-HF trial were evaluated every 2 to 8 weeks for the first 4 months and then every 4 months thereafter.[1] Once the patient is stable on the target daily dose of 400 mg, patients may only need to be monitored at a frequency similar as recommended for patients on ACE-I or ARB therapy.

Look-alike / Sound-alike Error Risk Potential: The Institute for Safe Medication Practice (ISMP) has not updated their List of Confused Drug Names since approval of sacubitril/valsartan.[28]

Pharmacology and Pharmacokinetic Properties:

Table 3. Basic Pharmacology and Pharmacokinetic Properties of Sacubitril/Valsartan.[12]

Parameter	
Mechanism of Action	Inhibition of neprilysin (neutral endopeptidase) via LBQ657, the active metabolite of the prodrug sacubitril, and blockade of the angiotensin II type-1 receptor and inhibition of angiotensin II-dependent aldosterone release via valsartan.
Oral Bioavailability	Sacubitril: ≥60%. Note: the valsartan in ENTRESTO is more bioavailable than the valsartan in other marketed tablet formulations; 26 mg, 51 mg, and 103 mg of valsartan in ENTRESTO is equivalent to 40 mg, 80 mg, and 160 mg of valsartan in other marketed tablet formulations, respectively.
Distribution and Protein Binding	The average apparent volumes of distribution of valsartan and sacubitril are 75 and 103 L, respectively. Sacubitril, LBQ657 and valsartan are highly bound to plasma proteins (94% to 97%).
Elimination	52% to 68% of sacubitril (primarily as LBQ657) and ~13% of valsartan and its metabolites are excreted in urine; 37% to 48% of sacubitril (primarily as LBQ657), and 86% of valsartan and its metabolites are excreted in feces.
Half-Life	Sacubitril, LBQ657, and valsartan are eliminated from plasma with a mean elimination half-life of approximately 1.4 hours, 11.5 hours, and 9.9 hours, respectively. Following twice-daily dosing of ENTRESTO, steady state levels of sacubitril, LBQ657, and valsartan are reached in 3 days.
Metabolism	Sacubitril is readily converted to LBQ657 by esterases; LBQ657 is not further metabolized to a significant extent. Valsartan is minimally metabolized; only about 20% of the dose is recovered as metabolites.

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Mortality (all-cause; secondary to cardiovascular causes)
2) Hospitalizations (secondary to cardiovascular causes)
3) Symptomatic relief (dyspnea on exertion, nocturnal dyspnea)
4) Quality of life

Primary Study Endpoint:
1) Composite (death from cardiovascular causes or first hospitalization from heart failure)

Table 4. Comparative Evidence of Sacubitril/Valsartan.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Quality Rating/ Risk of Bias/Applicability
1. PARADIGM-HF [1,13,29,30] MC, R, DB, AC PG	1. Sacubitril 97 mg/ valsartan 103 mg BID (200 mg BID) (S/V) 2. Enalapril 10 mg BID (E) Study Phases: i. Screening period ii. Single-blind enalapril run-in of 10 mg BID x2 wks iii. Single-blind LCZ696 run-in titration to 200 mg BID x4-6 wks iv. Randomized double-blind treatment to enalapril or LCZ696 27 months	Demographics: -Age: 64 y -Male: 78% -White: 66% -Asian: 18% -Black: 5% -NYHA class II: 70% -NYHA class III: 24% -NYHA class IV: 0.7% -LVEF: 29% -Ischemic etiology 60% -Beta-blocker: 94% -Diuretic: 82% -Aldosterone antagonist 58% -ICD/CRT 15% Inclusion Criteria: -Age ≥18 y -NYHA class II-IV -LVEF ≤35% -Hospitalization for HF last 12 months -Stable dose* of ACE-I/ARB and beta-blocker ≥4 wks Exclusion Criteria: -SBP <100 mmHg -h/o angioedema -Decompensated HF -eGFR <30 mL/min -K+ >5.2 mEq/L -ACS, CVA, TIA, PCI, cardiac or carotid surgery ≤3 m -Coronary or carotid disease *likely* to require surgery ≤6 m -Valvular disease -LV assistance device -Severe pulm disease -Life expectancy <5 y	mITT: S/V: n=4187 E: n=4212 Attrition: S/V: 17.8% E: 19.8%	Primary Endpoint: CV Death or Hospitalization for HF: S/V: 914 (21.8%) E: 1117 (26.5%) HR=0.80 (95% CI, 0.73-0.87; p<0.001) Secondary Endpoints: All-cause mortality: S/V: 17.0% vs. E: 19.8%; HR=0.84 (95% CI, 0.76-0.93; p<0.001) Change in KCCQ Score at 8 months (scale, 0-100): S/V: -2.99±0.36 vs. E: -4.63±0.36; mean difference=1.61 points (95% CI, 0.63-2.65; p=0.001)	4.7%/22 2.8%/36 NA	D/C due to AE: S/V: 10.7% E: 12.3% p=0.03 New Onset AFib: S/V: 3.1% E: 3.1% p=0.83 Symptomatic Hypotension: S/V: 14.0% E: 9.2% p<0.001 Hyperkalemia >6.0 mEq/L: S/V: 4.3% E: 5.6% p=0.007 Cough: S/V: 11.3% E: 14.3% p<0.001 Angioedema: (all severities) S/V: 19 (0.45%) E: 10 (0.24%) p=0.18 Decline in renal function (50% decline in eGFR, >30 mL/min decline if baseline eGFR <60 mL/min, or ESRD): S/V: 2.2% E: 2.6% p=0.28	1.6%/62 NS 4.8%/20 1.3%/76 3.0%/33 NS NS	**Quality Rating**: FAIR **Internal Validity (Risk of Bias)**: Selection: (low) allocation concealed through randomization by central IVRS;[31] baseline characteristics of both groups well balanced. Performance: (mod) match placebo provided to both groups in double-blind phase;[31] however, order of single-blind run-in phases poses risk of un-blinding after allocation. Detection: (low) blinded adjudication of outcomes; Attrition: (low) attrition similar between groups; data censored at last contact; modified ITT analysis. **Applicability**: Patient: only patients who tolerated both E 10 mg BID and S/V 200 mg BID were eligible for randomization. Extended run-in phases followed by 36-hr wash-out periods limit inferences to OHP population. Intervention: maintenance dose of S/V designed to yield systemic exposure of valsartan equal to 320 mg/d, the dose achieved in Val-HeFT[20] and VALIANT[21]; mean dose achieved was 375 mg/day. Comparator: enalapril dose similar to SOLVD Treatment trial;[22] mean dose was 18.9 mg/day. Valsartan a better comparison? Valsartan 320 mg/d may be superior to enalapril 20 mg/d when directly compared for various CV outcomes.[23–26] Outcomes: clinically relevant outcomes; composite primary endpoint driven by both outcomes equally; all-cause mortality composed mostly of CV deaths; Setting: Clinic visits every 2-8 weeks x4 months, and every 4 months thereafter.

Abbreviations [alphabetical order]: AC = active-controlled; ACE-I = ACE Inhibitors; ACS = acute coronary syndrome; AE = adverse events; AFib = atrial fibrillation; ARB = angiotensin receptor blockers; ARR = absolute risk reduction; CAD = coronary artery disease; CI = confidence interval; CRT = cardiac resynchronization therapy-defibrillator; CV = cardiovascular; CVA = stroke/transient ischemic attack; DB = double-blind; eGFR = estimated glomerular filtration rate (in mL/min/1.73 m^2); ESRD = end stage renal disease; h/o = history of; HR = hazard ratio; HTN = hypertension; ICD = implantable cardioverter-defibrillator; IVRS = interactive voice system response; K+ = potassium levels; KCCQ = Kansas City Cardiomyopathy Questionnaire (higher scores indicate better perceived health status and quality of life); LV = left ventricular; LVEF = left ventricular ejection fraction; m = months; MC = multi-centered; MI = myocardial infarction; mITT = modified intention to treat; n = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not significant; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PG = parallel-group; R = randomized; SBP = systolic blood pressure; y = years.

*Minimum Required Pre-study Daily Doses of Common ACE-Is or ARBs.

Enalapril 10 mg	Candesartan 16 mg
Captopril 100 mg	Irbesartan 150 mg
Fosinopril 20 mg	Losartan 50 mg
Lisinopril 10 mg	Olmesartan 10 mg
Moexipril 7.5 mg	Telmisartan 40 mg
Quinapril 20 mg	Valsartan 160 mg
Ramipril 5 mg	

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Appendix 1: Highlights of Prescribing Information[12]

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ENTRESTO safely and effectively. See full prescribing information for ENTRESTO.

ENTRESTO™ (sacubitril and valsartan) tablets, for oral use
Initial U.S. Approval: 2015

WARNING: FETAL TOXICITY
See full prescribing information for complete boxed warning.

- **When pregnancy is detected, discontinue ENTRESTO as soon as possible. (5.1)**
- **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. (5.1)**

----------INDICATIONS AND USAGE----------

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. (1.1)

ENTRESTO is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB. (1.1)

----------DOSAGE AND ADMINISTRATION----------

- The recommended starting dose of ENTRESTO is 49/51 mg (sacubitril/valsartan) twice-daily. Double the dose of ENTRESTO after 2 to 4 weeks to the target maintenance dose of 97/103 mg (sacubitril/valsartan) twice-daily, as tolerated by the patient. (2.1)
- Reduce the starting dose to 24/26 mg (sacubitril/valsartan) twice-daily for:
  - patients not currently taking an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) or previously taking a low dose of these agents (2.2)
  - patients with severe renal impairment (2.3)
  - patients with moderate hepatic impairment (2.4)

  Double the dose of ENTRESTO every 2 to 4 weeks to the target maintenance dose of 97/103 mg (sacubitril/valsartan) twice-daily, as tolerated by the patient. (2.2, 2.3, 2.4)

----------DOSAGE FORMS AND STRENGTHS----------

- Film-coated tablets (sacubitril/valsartan): 24/26 mg; 49/51 mg; 97/103 mg (3)

----------CONTRAINDICATIONS----------

- Hypersensitivity to any component. (4)
- History of angioedema related to previous ACE inhibitor or ARB therapy. (4)
- Concomitant use with ACE inhibitors. (4, 7.1)
- Concomitant use with aliskiren in patients with diabetes. (4, 7.1)

----------WARNINGS AND PRECAUTIONS----------

- Observe for signs and symptoms of angioedema and hypotension. (5.2, 5.3)
- Monitor renal function and potassium in susceptible patients. (5.4, 5.5)

----------ADVERSE REACTIONS----------

Adverse reactions occurring ≥5% are hypotension, hyperkalemia, cough, dizziness, and renal failure. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Dual blockade of the renin-angiotensin system: Do not use with an ACEi, do not use with aliskiren in patients with diabetes, and avoid use with an ARB. (4, 7.1)
- Potassium-sparing diuretics: May lead to increased serum potassium. (7.2)
- NSAIDs: May lead to increased risk of renal impairment. (7.3)
- Lithium: Increased risk of lithium toxicity. (7.4)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Breastfeeding or drug should be discontinued. (8.2)
- Severe Hepatic Impairment: Use not recommended. (2.4, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 7/2015

Sacubitril/Valsartan (Entresto™)

Goal(s):

- Restrict use of sacubitril/valsartan in populations and at doses in which the drug has demonstrated efficacy.
- Encourage use of beta-blockers with demonstrated evidence of mortality reduction in heart failure with reduced ejection fraction.

Length of Authorization:

- 60 days to 12 months

Requires PA:

- Sacubitril/valsartan (Entresto™)

Covered Alternatives:

- Preferred alternatives listed at http://www.orpdl.org/drugs/

Approval Criteria		
1. Is this a request for continuation of therapy (patient already on sacubitril/valsartan)?	Yes: Go to Renewal Criteria	No: Go to #2
2. What diagnosis is being treated?	Record ICD10 code.	
3. Does the patient have stable New York Heart Association Class II or III heart failure with reduced ejection fraction less than 40% (LVEF <40%)?	Yes: Go to #4	No: Pass to RPh. Deny for medical appropriateness
4. Has the patient tolerated a minimum daily dose an ACE-inhibitor or ARB listed in Table 1 for at least 30 days?	Yes: Go to #5	No: Pass to RPh. Deny for medical appropriateness

Approval Criteria		
5. Is the patient currently on a maximally tolerated dose of carvedilol, sustained-release metoprolol succinate, or bisoprolol; and if not, is there a documented intolerance or contraindication to each of these beta-blockers? *Note: the above listed beta-blockers have evidence for mortality reduction in chronic heart failure at target doses and are recommended by national and international heart failure guidelines.[1,2] Carvedilol and metoprolol succinate are preferred agents on the PDL.*	Yes: Approve for up to 60 days	No: Pass to RPh. Deny for medical appropriateness

Renewal Criteria		
1. Is the patient currently taking sacubitril/valsartan at the target dose of 97/103 mg 2-times daily?	Yes: Approve for up to 12 months	No: Pass to RPh and go to #2
2. What is the clinical reason the drug has not been titrated to the target dose of 97/103 mg 2-times daily?	Document rationale and approve for up to 60 days. Prior authorization required every 60 days until target dose achieved.	

Table 1. Minimum Daily Doses of ACE-inhibitors or ARBs Required.[1,2]

ACE-inhibitor		Angiotensin-2 Receptor Blocker (ARB)	
Captopril	50 mg TID	Candesartan	32 mg QDay
Enalapril	10 mg BID	Losartan	150 mg QDay
Lisinopril	20 mg QDay	Valsartan	160 mg BID
Ramipril	5 mg BID		
Trandolapril	4 mg QDay		

Abbreviations: BID = twice daily; QDay = once daily; mg = milligrams; TID = three times daily.

Notes:

- Patients must achieve a minimum daily dose of one of the drugs listed for at least 30 days in order to improve chances of tolerability to the target maintenance dose of sacubitril/valsartan 97/103 mg 2-times daily.[3]
- Valsartan formulated in the target maintenance dose of sacubitril valsartan 97/103 mg 2-times daily is bioequivalent to valsartan 160 mg 2-times daily.[4]
- ACE-inhibitors and ARBs listed have demonstrated efficacy in heart failure with or without myocardial infarction.[1,2]
- Target daily doses of other ACE-inhibitors and ARBs for heart failure have not been established.[1,2]
- It is advised that patients previously on an ACE-inhibitor have a 36-hour washout period before initiation of

sacubitril/valsartan to reduce risk of angioedema.[3,4]

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P&T / DUR Review: *09/15 (AG)*
Implementation: *TBD*