New Drug Evaluation: sacubitril/valsartan tablet, oral

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

End Date of Literature Search: July 1, 2015
Brand Name (Manufacturer): Entresto™ (Novartis)
Dossier Received: requested but not received

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-I and ARBs?
3. How well is sacubitril/valsartan tolerated in patients; and if available, how does the safety of sacubitril/valsartan compare to ACE-I 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-I or ARBs when used to manage chronic HFrEF?

Conclusions:
- There is low-to-moderate quality evidence from one study (PARADIGM-HF) with moderate risk of selection and performance bias that sacubitril/valsartan 97/103 mg twice daily (BID) reduces risk of death from CV causes or hospitalization for HF more than enalapril 10 mg BID alone (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 for 27 months). Patients were on recommended HF therapy (i.e., beta-blockers, diuretics, aldosterone antagonists) and had stable, mildly symptomatic HF (New York Heart Association II and III) with reduced ejection fraction (EF) equal to or less than 35%.1
- There is insufficient evidence to determine if the results observed in the PARADIGM-HF trial were driven by the maximum daily dose of valsartan (320 mg) or by the addition of a neprilysin inhibitor to a maximally dosed ARB. Evidence that directly compares sacubitril/valsartan to valsartan 320 mg daily is needed to determine whether sacubitril/valsartan should replace ACE-I s and ARBs for management of HFrEF.
- In patients with chronic HFrEF, there is moderate-quality evidence that sacubitril/valsartan 200 mg BID is superior to enalapril 10 mg BID at reducing all-cause mortality (17.0% vs. 19.8%; HR=0.84 [95% CI, 0.76-0.93; p<0.001]). These results correlate with a number needed-to-treat (NNT) of 36 over about 2 years to prevent 1 death.
- There is low-quality evidence that sacubitril/valsartan is similar to enalapril at reducing HF symptoms and the physical limitations of HFrEF when assessed using the validated Kansas City Cardiomyopathy Questionnaire (KCCQ).1 The difference in KCCQ scores were statistically significant when assessed at 8 months (difference of 1.61 points on a 100-point scale),1 but much larger differences are needed to be clinically meaningful to the patient.2,3
- There is low-quality evidence that sacubitril/valsartan does not increase risk of new onset atrial fibrillation or decrease kidney function compared to enalapril alone.1 Sacubitril/valsartan at a maintenance dose of 200 mg BID is tolerated similarly to enalapril 10 mg BID, but is associated with more episodes

Author: A. Gibler, Pharm.D. Date: September 2015
of symptomatic hypotension. However, sacubitril/valsartan is also associated with less cough and less incidence of severe hyperkalemia (>6.0 mEq/L) than enalapril.

- There is insufficient evidence of a dose-response for sacubitril/valsartan; therefore, a daily 400 mg dose needs to be achieved to expect the mortality and morbidity benefits observed in the Phase 3 clinical 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-naive patients. Consistent with most HF studies, Blacks were also underrepresented in this trial despite the high prevalence of HF in this population.

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

**Background:**
The goals of management of HFrEF (i.e., systolic HF) are to relieve symptoms (e.g., dyspnea) and signs (e.g., edema), typically with diuretics, and to prevent hospital admission and improve survival. The cornerstone of drug therapy in chronic HFrEF is the inhibition of the neurohormonal activation that plays such a large role in the pathophysiology and progression of HF. Standard drug treatment proven to reduce all-cause mortality for all chronic HFrEF patients (NYHA class I-IV) includes an ACE-I (alternatively, an ARB if an ACE-I is not tolerated) and 1 of the 3 beta-blockers proven to reduce mortality (bisoprolol, carvedilol, or sustained-release metoprolol succinate). Both an ACE-I and a beta-blocker should be initiated as soon as HFrEF is diagnosed. An ACE-I can reduce mortality and hospitalizations, improve symptoms, exercise tolerance and performance, and improve quality of life in patients with HFrEF. The benefits of ACE inhibition are seen in patients with mild, moderate or severe symptoms of HF and in patients with or without CAD. The available data suggest there are no differences between ACE-I or between ARBs in their effect on symptom improvement and survival. The addition of a beta-blocker to an ACE-I further improves morbidity and mortality in these patients. Besides also reducing mortality and hospitalizations, long-term treatment with the aforementioned beta-blockers can improve symptoms of HF, improve functional status, and enhance the patient’s overall sense of well-being. However, these benefits should not be considered a class effect. Other beta-blockers, including metoprolol tartrate, were less effective in HF trials. 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.

Aldosterone receptor antagonists (spironolactone, eplerenone) 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. 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. However, renal function and potassium should be routinely monitored because of their risk for life-threatening hyperkalemia, especially in the presence of worsening renal function. Other therapeutic options include hydralazine and isosorbide dinitrate, which have shown to decrease morbidity and mortality in Black patients with NYHA class III-IV and reduced EF. 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). In Europe, consideration for ivabradine (approved by European Medicines Agency in 2005) 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 receptor antagonist.

Author: A. Gbler, Pharm.D. Date: September 2015
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). Patients do not need to be on a target ACE-I dose before initiation of beta-blocker therapy. Even in patients on a low dose of an ACE-I, the addition of a beta blocker produces a greater improvement in symptoms and mortality reduction than increasing the dose of the ACE-I alone, even to the target doses used in clinical trials.

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

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

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.

Inhibition of the renin-angiotensin-aldosterone system (RAAS) has led to effective management of HFREF. Cardiac remodeling observed in both infarcted and non-infarcted myocardium is recognized as a major factor in the development of impaired LV dysfunction. Cardiac remodeling involves molecular and cellular changes to the cardiomyocytes and the interstitium which results structural and functional changes to the heart. Cardiac dilatation, interstitial fibrosis, and reduction in contractility and relaxation are all consequences of cardiac remodeling. Angiotensin II plays a role in the pathogenesis of myocardial repair and remodeling by promoting production of reactive oxygen species and the synthesis specific growth factors. ACE-Is have a profound effect on the neurohormonal state of patients with HF by blocking both the conversion of angiotensin I to angiotensin II and the breakdown of bradykinin. RAAS inhibitors moderate vasoconstriction, myocyte hypertrophy, and myocardial fibrosis, of which the effects result in clinically meaningful improvements in patient symptoms and function. However, other than ACE-Is, ARBs, aldosterone antagonists, and direct renin inhibitors all have varying levels of evidence for HF but offer potential targets for further research in this population.

Nepriyisn inhibitors were first investigated as a therapeutic strategy in HF in the 1990s. Nepriyisn is a neutral endopeptidase that degrades vasoactive peptides such as natriuretic peptides and bradykinin. 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). Natriuretic peptides have potent natriuretic properties, also inhibits RAAS, and reduce sympathetic drive. Thus, inhibiting nepriyisn increases the levels of these peptides and counters the neurohormonal activation associated with vasoconstriction, sodium retention and cardiac remodeling. However, the combined use of an ACE-I and a nepriyisn inhibitor (enalapril/omapatrilat) was associated with serious angioedema when studied in HF. Subsequently, sacubitril, a prodrug converted into the nepriyisn inhibitor LBQ657, was studied in combination with an ARB (valsartan) in patients with HFREF in the PARADIGM-HF trial. Evidence from this trial was used by the U.S. Food and Drug Administration (FDA) to grant approval for its use in July 2015. 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. Sacubitril/valsartan is a first-in-class angiotensin receptor nepriyisn inhibitor (ARNI). After ingestion, the drug delivers systemic exposure of sacubitril, a nepriyisn inhibitor pro-drug, and valsartan. Sacubitril is rapidly metabolized by esterases to the active nepriyisn inhibitor LBQ657. The total daily 400 mg maintenance dose of

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Date: September 2015
SACUBITRIL/VALSARTAN

SACUBITRIL/VALSARTAN approved by the FDA contains only 206 mg of valsartan but yields systemic exposures similar to 320 mg per day due to increased bioavailability from this formulation.13

In HF patients with preserved EF (HFP EF), 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 HFP EF (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%). The investigators used a careful, step-wise approach to their study to maximize safety, but might limit the generalizability of the initiation of this drug in the general HF population. First, there was a screening period to assess patient eligibility based on several 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 eligible patients who could tolerate the target dose of enalapril could tolerate a target dose of sacubitril/valsartan 200 mg BID. About 20% of the patients eligible based on inclusion and exclusion criteria were not eligible for the clinical trial – mostly because of intolerance to either target doses of enalapril or target doses of sacubitril/valsartan. 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. Thus, the investigators used an innovative approach: instead of adding new therapy to standard of care, the investigators proposed substituting a cornerstone of HF therapy, an ACE-I, for sacubitril/valsartan.

Baseline characteristics were similar between the groups. Overall, the population studied had stable, mildly symptomatic HFrEF on recommended HF therapy. 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.

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

Author: A. Gibler, Pharm.D.

Date: September 2015
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, which is a validated way for patients to measure their physical functioning, symptoms and quality of life,7 improved by 1.61 points (scale, 0-100) with sacubitril/valsartan compared to enalapril. However, variation of up to 4 points are frequently observed in stable HF patients2 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 felt better 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.17

The internal validity of the study was compromised by some troublesome omissions that introduce bias. The method of randomization was not clearly stated and it is difficult to assess whether group allocation remained concealed to all parties involved in the study. Fortunately, baseline characteristics were well matched which obviates some concern. The single-blinded run-in phases, however, compromise both internal validity and applicability. Patients and investigators can familiarize themselves to the effects of a specific treatment which may compromise blinding of therapy after randomization to the respective treatment arm. These run-in phases, though needed to assess tolerability in order to minimize attrition after randomization, complicate the initiation of this drug in the general HF population, especially with providers unfamiliar with the evidence of HF therapy. It is also not clear if the efficacy of sacubitril/valsartan can be attributed to the addition of the nepriylin inhibitor to an ARB, or if it was the maximum recommended dose of valsartan utilized in the study. Though the doses of valsartan and enalapril are appropriate in this study,18–20 a comparison sacubitril/valsartan to valsartan 320 mg daily would be helpful to explain the benefits of sacubitril/valsartan observed. An ACE-I is preferred to an ARB for management of HF based on mortality data; however, when valsartan has been directly compared to enalapril in various populations, outcomes studied show that a daily 40 mg dose of enalapril may have been a reasonable comparator.21–24 Lastly, early termination of randomized controlled trials tend to exaggerate differences between comparator groups.25 Though we have long-term evidence for ACE-I,s the long-term safety and efficacy of sacubitril/valsartan remains to be seen.

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.

Author: A. Gibler, Pharm.D. Date: September 2015
Table 2. Adverse Reactions Reported in ≥5% of Patients Treated with Sacubitril/Valsartan in PARADIGM-HF.12

<table>
<thead>
<tr>
<th></th>
<th>Sacubitril/Valsartan (n=4,203)</th>
<th>Enalapril (n=4,229)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>18%</td>
<td>12%</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>12%</td>
<td>14%</td>
</tr>
<tr>
<td>Cough</td>
<td>9%</td>
<td>13%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Renal Failure/Acute Renal Failure</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>

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.26

Pharmacology and Pharmacokinetic Properties:

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of Action</td>
<td>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.</td>
</tr>
<tr>
<td>Oral Bioavailability</td>
<td>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.</td>
</tr>
<tr>
<td>Distribution and Protein Binding</td>
<td>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%).</td>
</tr>
<tr>
<td>Elimination</td>
<td>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.</td>
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<tr>
<td>Half-Life</td>
<td>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.</td>
</tr>
<tr>
<td>Metabolism</td>
<td>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.</td>
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</tbody>
</table>

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**Comparative Clinical Efficacy:**

Clinically Relevant Endpoints:
1) Mortality (all-cause; secondary to cardiovascular causes)
2) Hospitalizations (secondary to cardiovascular causes)
3) Symptom-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.

<table>
<thead>
<tr>
<th>Ref./Study Design</th>
<th>Drug Regimens/Duration</th>
<th>Patient Population</th>
<th>N</th>
<th>Efficacy Endpoints</th>
<th>ARR/NNT</th>
<th>Safety Outcomes</th>
<th>ARR/NNH</th>
<th>Quality Rating/Internal Validity Risk of Bias/Applicability Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. LCZ696 200 mg BID (sacubitril 97 mg/valsartan 103 mg) (S/V)</td>
<td>Demographics: Mean Age: 64 y Males: 78% Whites: 66% Asians: 18% Blacks: 5% NYHA class I: 5% NYHA class II: 70% NYHA class III: 24% NYHA class IV: 1% Mean LVEF: 29% Beta-blocker: 93% Diuretic: 80%</td>
<td>mITT: S/V: n=4187 E: n=4212</td>
<td>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&lt;0.001)</td>
<td>D/C due to AE: S/V: 10.7% E: 12.3% p=0.03</td>
<td>New Onset AFib: S/V: 3.1% E: 3.1% p=0.83</td>
<td>Symptomatic Hypotension: S/V: 14.0% E: 9.2% p&lt;0.001</td>
<td>Hyperkalemia &gt;6.0 mEq/L: S/V: 4.3% E: 5.6% p=0.007</td>
<td>Cough: S/V: 11.3% E: 14.3% p&lt;0.001</td>
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<tr>
<td>2. Enalapril 10 mg BID (E)</td>
<td>Inclusion Criteria: -Age ≥18 y -NYHA class II-IV -LVEF ≥50% -On ACE-I/ARB equiv to enalapril 10 mg/d or higher* -On beta-blocker (unless contraindicated)</td>
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<td>Exclusion Criteria: -SBP &lt;100 mmHg -h/o angioedema - Decompensated HF -eGFR &lt;30 mL/min -K+ &gt;5.2 mEq/L -Recent ACS, CVA, TIA, PCI, cardiac or carotid surgery -significant mitral or aortic valve disease except mitral regurgitation from LV dilatation -LV assistance device</td>
<td></td>
<td>Secondary Endpoints: All-cause mortality: S/V: 17.0% vs. E: 19.8%; HR=0.84 (95% CI, 0.76-0.93; p&lt;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)</td>
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<td></td>
<td>Attrition: S/V: 17.8% E: 19.8%</td>
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<td>3. HeFT18</td>
<td>E: 103</td>
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<tr>
<td></td>
<td>1.3%/76</td>
<td>3.0%/33</td>
<td>1.6%/62</td>
<td>NS</td>
<td>NS</td>
<td>4.8%/20</td>
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</table>

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**Date:** September 2015

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**Study Phases:**

- **Screening period**
- **Single-blind enalapril run-in of 10 mg BID x2 wks**
- **Single-blind LCZ696 run-in titration to 200 mg BID x4-6 wks**
- Randomized double-blind treatment to enalapril or LCZ696  

- **27 months**
**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; CI = confidence interval; CV = cardiovascular; CVA = stroke/transient ischemic attack; DB = double-blind; eGFR = estimated glomerular filtration rate (in mL/min/1.73 m²); ESRD = end stage renal disease; h/o = history of; HR = hazard ratio; K+ = potassium levels; KCCQ = Kansas City Cardiomyopathy Questionnaire (with higher scores indicated more severe heart failure symptoms and limitations); LCZ696 = sacubitril/valsartan; LV = left ventricular; LVEF = left ventricular ejection fraction; MC = multi-centered; 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.

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril 10 mg</td>
<td>Candesartan 16 mg</td>
</tr>
<tr>
<td>Captopril 100 mg</td>
<td>Irbesartan 150 mg</td>
</tr>
<tr>
<td>Fosinopril 20 mg</td>
<td>Losartan 50 mg</td>
</tr>
<tr>
<td>Lisinopril 10 mg</td>
<td>Olmesartan 10 mg</td>
</tr>
<tr>
<td>Moexipril 7.5 mg</td>
<td>Telmisartan 40 mg</td>
</tr>
<tr>
<td>Quinapril 20 mg</td>
<td>Valsartan 160 mg</td>
</tr>
<tr>
<td>Ramipril 5 mg</td>
<td></td>
</tr>
</tbody>
</table>
References:


Author: A. Gibler, Pharm.D.  Date: September 2015


Author: A. Gibler, Pharm.D.

Date: September 2015
Appendix 1: Highlights of Prescribing Information

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 ---
Appendix 2: Proposed Prior Authorization Criteria

**Sacubitril/Valsartan**

**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

**Covered Alternatives:**
- Preferred alternatives listed at [http://www.orpdl.org/drugs/](http://www.orpdl.org/drugs/)

<table>
<thead>
<tr>
<th>Approval Criteria</th>
<th>Yes: Go to Renewal Criteria</th>
<th>No: Go to #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is this a request for continuation of therapy (patient already on sacubitril/valsartan)?</td>
<td>Yes: Go to Renewal Criteria</td>
<td>No: Go to #2</td>
</tr>
<tr>
<td>2. What diagnosis is being treated?</td>
<td>Record ICD9 code.</td>
<td></td>
</tr>
<tr>
<td>3. Does the patient have stable New York Heart Association Class II-III heart failure with reduced ejection fraction equal to or less than 35% (LVEF ≤35%)?</td>
<td>Yes: Go to #4</td>
<td>No: Pass to RPh. Deny for medical appropriateness</td>
</tr>
<tr>
<td>4. Has the patient tolerated a target daily dose* of an ACE-inhibitor or ARB for at least 30 days?</td>
<td>Yes: Go to #5</td>
<td>No: Pass to RPh. Deny for medical appropriateness</td>
</tr>
</tbody>
</table>
### Approval Criteria

5. Is the patient currently on a maximally tolerated dose of carvedilol, sustained-release metoprolol succinate, or bisoprolol?  
   - Yes: Approve for up to 60 days  
   - No: Go to #5  
   
   *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.

6. Does the patient have a documented contraindication to carvedilol, sustained-release metoprolol succinate, or bisoprolol?  
   - Yes: Document contraindication and approve for up to 60 days  
   - No: Pass to RPh. Deny for medical appropriateness

### Target Daily Doses of ACE-inhibitors or ARBs with Demonstrated Efficacy in Heart Failure.\(^1,2\)

<table>
<thead>
<tr>
<th>ACE-inhibitors</th>
<th>Target Daily Dose</th>
<th>ARBs</th>
<th>Target Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>150 mg</td>
<td>Candesartan</td>
<td>32 mg</td>
</tr>
<tr>
<td>Enalapril</td>
<td>20-40 mg</td>
<td>Losartan</td>
<td>150 mg</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>40 mg</td>
<td>Valsartan</td>
<td>320 mg</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>20-40 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perindopril</td>
<td>8-16 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinapril</td>
<td>40 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ramipril</td>
<td>10 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trandolapril</td>
<td>4 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Renewal Criteria

1. Is the patient currently taking sacubitril/valsartan at the target dose of 200 mg (97/103 mg) 2-times daily?  
   - Yes: Approve for up to 1 year  
   - 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 200 mg (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.

### References:
