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Drug Class Update with New Drug Evaluation: Heart Failure Therapy Focused Update of Sacubitril/Valsartan

Date of Review: June 2021

Date of Last Review: May 2017
Dates of Literature Search: 03/01/2017 – 01/31/2021
Brand Name (Manufacturer): Verquvo® (Merck)
Dossier Received: yes

Generic Name: Vericiguat

Current Status of PDL Class: See **Appendix 1**.

Purpose for Class Update:
To review new evidence for efficacy and harms of sacubitril/valsartan in the treatment of chronic heart failure (HF), including evidence supporting its expanded indication for all patients with chronic heart failure, across the spectrum of ejection fraction (EF). This review will also evaluate the evidence and place in therapy of vericiguat in the treatment of heart failure with reduced ejection fraction (HFrEF).

Research Questions:
1. What is the evidence for sacubitril/valsartan to reduce mortality and cardiovascular (CV) morbidities when used to manage chronic heart failure with heart failure with preserved ejection fraction (HFpEF)?
2. Are there subgroups of patients in which sacubitril/valsartan may be safer or more effective when used to manage chronic HFpEF?
3. What is the evidence for vericiguat to reduce mortality and CV morbidities when used to manage chronic HFrEF?
4. What are the safety and harms of vericiguat; and if available, how do these compare to the safety and harms of ACE-inhibitors (ACE-Is) and angiotensin II receptor blockers (ARBs) when used to manage chronic HFrEF?
5. Are there subgroups of patients in which vericiguat may be safer or more effective when used to manage chronic HFrEF?

Conclusions:
- There is insufficient evidence that sacubitril/valsartan reduces CV outcomes in patients with HFpEF. There was no significant difference in the composite of CV death or total heart failure (HF) hospitalizations in a phase 3, double-blind, active comparator, randomized controlled trial in adults with symptomatic HF and a left ventricular ejection fraction ≥ 45%.[1] The effect of sacubitril/valsartan on the primary endpoint was driven primarily by the total HF hospitalizations component.
- Subgroup analyses of this trial for the primary efficacy endpoint showed that subjects with a left ventricular ejection fraction (LVEF) below the median (LVEF 57%) appeared to be more beneficial (rate ratio [RR] 0.78, 95% CI 0.64-0.95) than with an LVEF above the median (RR 1.00, 95% CI 0.81-1.23). [1] The FDA labeling notes that benefits are most clearly evident in patients with LVEF below normal. Additionally, sacubitril/valsartan seemed to reduce the risk of HF hospitalization in women more than men.

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- There is insufficient evidence that sacubitril/valsartan reduces CV outcomes or improves quality of life in pediatric patients with HFrEF. There is low quality evidence based on a 12-week interim analysis of a 52-week RCT that sacubitril/valsartan results in a mean percent reduction in N-terminal -proB natriuretic peptide (NT-proBNP) of 44%, similar to the reduction seen in adults in clinical trials, but was not statistically superior to the reduction seen with enalapril. [2]
- There is moderate quality evidence that vericiguat reduces CV death or HF hospitalization compared to placebo (35.5% vs. 38.5%; Hazard Ratio [HR] 0.90; 95% CI 0.82 to 0.98; Number Needed to Treat [NNT] 34) in patients with symptomatic advanced HFrEF on goal directed medical therapy with a recent decompensation and elevated NT-proBNP but does not reduce all-cause mortality. [3]
- There is low quality evidence of no significant difference in discontinuations due to adverse events between vericiguat and placebo, but a higher rate of hypotension and anemia. [3] Vericiguat is contraindicated in pregnancy and should not be used with long-acting nitrates or phosphodiesterase type 5 (PDE5) inhibitors due to its effects on the nitric oxide pathway. An unknown safety concern includes its higher rate of CV death and hospitalization among subjects with the highest baseline NT-proBNP levels in the clinical study.[3]

Recommendations:
- Rename the "ACEIs, ARBs and DRIs" PDL class to "Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)" and include sacubitril/valsartan as a non-preferred agent in the class.
- Update prior authorization criteria for sacubitril/valsartan to include expanded FDA indications (**Appendix 6**).
- Maintain vericiguat as non-preferred and require prior authorization (**Appendix 6**) to ensure appropriate use in patients on goal directed therapy with advanced symptomatic HFrEF.

Summary of Prior Reviews and Current Policy
- 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 HFrEF 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).[4]
- 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).[4]
- 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
- Current prior authorization limits use of sacubitril/valsartan to patients with HFrEF with ejection fraction <40%, on maximally tolerated ACE-I or ARB and a recommended beta-blocker.

Background:
Heart failure (HF) is a clinical syndrome caused by a structural and/or functional cardiac abnormality, resulting in reduced cardiac output and/or elevated cardiac pressures. It results in symptoms such as edema, shortness of breath and fatigue and is often recognized by signs of elevated jugular venous pressure, pulmonary crackles, and pulmonary edema. Heart failure is further classified into HFrEF (left ventricular ejection fraction ≤ 40%) and HFpEF (left ventricular ejection fraction > 50%). [5] A left ventricular ejection between 41% and 49% is referred as heart failure with mid-range ejection fraction (HFmrEF). The goals of management of HFrEF are to prevent hospital admission and improve survival, and to relieve signs (e.g., edema) and symptoms (e.g., dyspnea). The cornerstone of drug therapy in chronic HFrEF is inhibition of the neurohormonal activation present in HFrEF that promotes cardiac remodeling.[5,6] The most well-studied

system is the renin-angiotensin-aldosterone system (RAAS), and inhibition of RAAS has been shown to have a significant impact on the pathophysiology and progression of HF.[5,6] Drugs that inhibit neurohormonal activation in HFrEF have consistently proven to reduce all-cause mortality in chronic HFrEF patients (NYHA class I-IV).[7] These drugs include an ACE-I (alternatively, an ARB if an ACE-I is not tolerated), a cardioselective beta-blocker (bisoprolol, carvedilol, or sustained-release metoprolol succinate), and for most patients, a mineralocorticoid (aldosterone) receptor antagonist (spironolactone or eplerenone).

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 coronary artery disease (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 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 20-40 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, but there is no substantive placebo-controlled RCT and the optimum dose is uncertain.

Ventricular diastolic dysfunction is the main characteristic in HFpEF, likely caused by hypertensive left ventricular remodeling.[8] Atrial fibrillation occurs commonly with HFpEF, and up to 30% of patients may have normal levels of natriuretic peptides. Patients with HFpEF tender to be older and more commonly women compared to HFrEF. Unlike in HFrEF, no therapy has been shown to improve outcomes in patients with HFpEF. Current treatment strategies including symptomatic management of volume overload and controlling coexisting conditions such as hypertension and atrial fibrillation.[8] Therapy with ACE-I/ARBs and beta-blockers are limited for use in HFpEF to those who have alternative indications. Spironolactone has been shown to reduce the rate of heart failure hospitalizations but had no significant effect on all-cause mortality or hospitalizations from any cause.[8]

Neprilysin is a neutral endopeptidase that degrades vasoactive peptides such as natriuretic peptides and bradykinin.[9] Natriuretic peptides, which include atrial natriuretic peptide and B-type natriuretic peptide (BNP), are secreted by the heart in response to increased cardiac wall stress (and also secreted by other organs in response to other stimuli).[9] Inhibition of neprilysin increases the levels of these peptides and counteracts the neurohormonal activation associated with vasoconstriction, sodium retention and cardiac remodeling. However, the combined use of an ACE-I and a neprilysin inhibitor (enalapril/omapatrilat) was associated with serious angioedema when studied in HF. Subsequently, sacubitril, a prodrug converted into the neprilysin inhibitor sacubitrilat, was studied in combination with an ARB (valsartan) in patients with HFrEF in the PARADIGM-HF trial.[4] Sacubitril/valsartan is a first-in-class angiotensin receptor neprilysin inhibitor (ARNI). The PARADIGM-HF trial provided moderate quality evidence that sacubitril/valsartan 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; HR=0.80 (95% CI 0.73 to 0.87; p<0.001; NNT 22)].[4] Additionally, sacubitril/valsartan was associated with more episodes of symptomatic hypotension than enalapril (14.0% vs. 9.2%, respectively), but a lower incidence of cough and hyperkalemia.[4] In February 2021, the FDA label for sacubitril/valsartan was expanded and includes "to reduce the risk of CV death and HF hospitalization in adults patients with chronic HF (including HFpEF)".[10] Current HF guidelines recommend use of sacubitril/valsartan for patients with HFrEF who remain symptomatic despite optimal medical therapy with an ACE-I or ARB, and beta-blocker.[11] The pivotal trials required run-in periods demonstrating tolerance to ACE-I or ARB therapy prior to initiation of sacubitril/valsartan.

In addition to sacubitril/valsartan, additional therapies have been evaluated in chronic heart failure, including sodium-glucose cotransporter-2 (SGLT2) inhibitors and vericiguat (**Tables 2 and 3**). Vericiguat is a soluble guanylate cyclase (sGC) stimulator, causing vasodilation through the nitric oxide pathway.

Table 2: Characteristics of Cardiovascular Outcome trials for Newer Therapies for chronic Heart Failure[1,3,4,12,13]

	PARADIGM-HF	PARAGON-HF	EMPEROR-Reduced	DAPA-HF	VICTORIA
Study Drug	Sacubitril/Valsartan	Sacubitril/Valsartan	Empagliflozin	Dapagliflozin	Vericiguat
Patient Population	HFrEF (EF ≤ 35%)	HFpEF (EF ≥ 45%)	HFrEF (EF ≤ 40%)	HFrEF (EF ≤ 40%)	HFrEF (EF ≤ 45%) with worsening HF
Comparator	Enalapril	Valsartan	Placebo	Placebo	Placebo
Mean LVEF	29%	58%	27%	31%	29%
NYHA III-IV	25%	19%	25%	33%	41%
Median Follow-up	27 months	35 months	16 months	18 months	11 months

Abbreviations: EF: ejection fraction; HF: heart failure, HFrEF: heart failure with reduced ejection fraction, HFpEF: heart failure with preserved ejection fraction, LVEF: left ventricular ejection fraction; NYHA: New York Heart Association class

Table 3: Summary of Results from Cardiovascular Outcome Trials in HFrEF[1,3,4,12,13]

Outcome	Sacubitril/Valsartan ARR/NNT	Empagliflozin ARR/NNT	Dapagliflozin ARR/NNT	Vericiguat ARR/NNT
CV death and heart failure hospitalization*	4.7% / 22	5.3% / 19	4.9% / 21	3%/ 34
Death from any cause	2.8% / 36	NS	2.3% / 44	NS
CV Death	3.2% / 32	NS	1.9% / 53	NS

Abbreviations: ARR: absolute risk reduction; CV: cardiovascular; NNT: number needed to treat; NS: not significant
*analyzed as time to first event

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
After review, 3 systematic reviews[14-16] were excluded due to poor quality[14-16] (e.g, indirect network-meta analyses), wrong study design of included trials (e.g., observational)[17], comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical)[18]. One systematic review from the Cochrane Collaboration evaluating the efficacy of beta-blockers and inhibitors of the RAAS for HFpEF was identified.[19] However, at the time there were no completed studies available with sacubitril/valsartan in HFpEF.

New Guidelines:
Three guidelines were excluded due to poor quality rigor of development and systematic approach.[7,20,21] Two of these are consensus statements.[7,20]

<u>American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA): Focused Update of the 2013 Guideline on the Management of Heart Failure[11]</u>

The 2017 focused update of the 2013 guideline included revisions on biomarkers, new therapies for HFrEF, updates on HFpEF and new data on important comorbidities. Part 1 of this guideline included an update on new pharmacological therapy, including sacubitril/valsartan in HFrEF, and was reviewed in a previous class update. There were no major changes to recommendations regarding therapy with an ARNI in this update. There remains a Class I recommendation based on level B-R evidence that in patients with chronic symptomatic HFrEF who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality. An ARNI should not be administered concomitantly with ACE-I or within 36 hours of the last dose due to the risk of angioedema.

<u>National Institute for Health and Care Excellence (NICE): Chronic heart failure in adults: diagnosis and management.[22]</u>

The NICE updated its guidelines for chronic heart failure in adults in 2018. Recommendations were based on systematic reviews of best available evidence and consideration of cost effectiveness. The guideline recommendations were intended for primary care clinicians. The guidelines recommend first-line therapy with an ACE-I and beta blocker for those patients with HFrEF. The following are key guideline statements regarding therapy with sacubitril/valsartan:

- Sacubitril/valsartan is recommended as an option for treatment symptomatic chronic HFrEF, only in people:
    - With NYHA class II to IV symptoms, and
    - Left ventricular ejection fraction of 35% or less, and

- Who are already taking a stable dose of an ACE-I or ARB
- Treatment with sacubitril/valsartan should be started by a heart failure specialist with access to a multidisciplinary heart failure team

New Formulations or Indications:

- In October 2019, the FDA labeling for sacubitril/valsartan was expanded to include pediatric patients age 1 year and older with heart failure and systemic left ventricular systolic dysfunction.[2] This expanded approval was based on a 12-week analysis of the 52-week PANORAMA-HF study. The PANORAMA-HF trial was a two-part, multi-center, randomized, double-blind, parallel group, 52-week study.[23] This trial remains unpublished and cannot fully be assessed for quality and risk of bias. Key inclusion criteria included children aged 1-17 years with chronic heart failure due to left ventricular systolic dysfunction (LVEF ≤40%) previously on an ACE or ARB. Key exclusion criteria included patients with a single ventricle or systemic right ventricle, patients listed for heart transplant, with sustained or symptomatic dysrhythmias, with restrictive or hypertrophic cardiomyopathy, active myocarditis, history of angioedema, moderate-to-severe obstructive pulmonary disease, and serum potassium >5.3 mmol/L. Phase one was a pharmacokinetic study to that demonstrated similar exposure in pediatric patients with studied doses (3.1 mg/kg) as adults on 97/103 mg of sacubitril/valsartan.

  Phase 2 of the study evaluated the efficacy and safety of sacubitril/valsartan (target dose 3.1 mg/kg BID) compared to enalapril (target dose 0.2 mg/kg BID) in pediatric HF patients. The primary efficacy outcome was originally designed using a Global Rank endpoint including death, listing for heart transplant, worsening of heart failure and quality of life. However, due to challenges with recruitment, the NT-proBNP was used as a bridging biomarker to evaluate clinical efficacy. The interim analysis for primary efficacy was designed to demonstrate a 30% or greater reduction in NT-proBNP from baseline at week 12 for sacubitril/valsartan compared to enalapril.

  At week 12, sacubitril/valsartan (n=54) resulted in a 15.6% greater reduction than enalapril (n=54) (adjusted geometric mean ratio 0.84; 95% CI 0.67-1.06) for the mean ratio of NT-proBNP to baseline levels but did not reach superiority over enalapril. FDA analysis noted that the mean percent reduction at week 12 (44%) was similar to reduction seen in adults in the PARADIGM-HF trial. [2] There was less of a treatment response seen in the subgroup of patients age 1 to < 6 years old. Results at 52 weeks are not available.

- In February 2021, sacubitril/valsartan was FDA approved for all patients with chronic HF, including those with HFpEF.[10] This expanded approval was based on the results of the PARAGON-HF trial.

  The PARAGON-HF trial **(Table 4)** was a multi-center, randomized, double-blind active comparator trial in 43 countries.[1] The trial evaluated the efficacy of sacubitril/valsartan in patients with symptomatic heart failure and an ejection fraction of 45% or higher, including both those with mildly reduced and normal LVEF. The primary endpoint was the composite of total heart failure hospitalizations and death from CV causes. Total number of hospitalizations was used instead of the more common time-to-first event analysis since patients with HFpEF have a higher rate of hospitalizations and lower rate of CV death compared to patients with HFrEF. The trial contained a pre-randomization run-in period of an average of 14 days of valsartan, followed by an average of 19 days of sacubitril/valsartan to assess for tolerability. After the run-in, patients were randomized to a target dose of valsartan 160 mg twice daily or a target dose of sacubitril-valsartan 97/103 mg twice daily. Only individuals who tolerated sacubitril/valsartan 49/51 mg twice daily were eligible for randomization. Overall, there was no significant difference in the primary outcome of total HF hospitalizations and CV death with 12.8 events per 100 patient-yr in the sacubitril/valsartan group and 14.6 per 100 patient-year in the valsartan group (RR 0.87; 95% CI 0.75 to 1.01). This endpoint was primarily driven by the rate of HF hospitalizations. Based on the power calculation, the difference in events between groups was smaller than anticipated.

While the primary endpoint was found to be non-significant, the FDA determined that the primary endpoint was primarily driven by the reduction in heart failure hospitalizations, whereas the CV death endpoint approached neutrality.[24] The FDA was intrigued by the subgroup analysis which determined those with moderately reduced ejection fraction below the median (≤ 57%) appeared to receive benefit from sacubitril/valsartan more than those with a higher ejection fraction with a rate ratio of 0.78 (95% CI 0.64 to 0.95), which is consistent with the PARADIGM trial results.[1,24] The applicant (Novartis) determined a possible cause for non-significant results in PARAGON could be due to rejection of primary events during adjudication due to an effort to maximize specificity for the primary efficacy endpoint. They also reported that more flexibility in clinical judgement would have reversed some of the diagnoses. The clinical events committee used strict criteria for adjudicating hospitalizations for heart failure, which may have reduced event counts due to insufficient documentation. The FDA review of the new indication asked the applicant to re-evaluate events which were possibly rejected as a primary endpoint event and determine a probability that these endpoints which, while marked negative for the trial, may have been positive events. After re-analysis of events from investigator rather than clinical events committee, the primary endpoint was found to have a rate ratio of 0.84 (95% CI 0.74 to 0.97, p=0.014).[24] The pre-specified exploratory expanded composite endpoint adding urgent care visits (RR 0.86; 95% CI 0.75-0.99; p=0.04) and re-adjudication analysis of unconfirmed HF hospitalizations (RR 0.86; 95% CI 0.75-1.00; p=0.04) contributed to the FDA decision along with evidence from the PARADIGM-HF study.[24]

The trial was funded by Novartis and found to have a low risk of bias. The pre-randomization run in periods increase the risk of unblinding and exclude high risk individuals who may experience adverse events. A total of 5746 participants entered the valsartan phase with 541 discontinuations (9.4%), and 5205 participants entered the sacubitril/valsartan phase with 384 discontinuations (7.3%).[1] Generalizability and applicability of study results remains limited based on no difference between the treatment group and placebo. Since patients with HFpEF have lower circulating neprilysin levels, a neprilysin inhibitor may be less effective. While the investigators did report a change in quality of life, as measured by the Kansas City Cardiomyopathy questionnaire (KCCQ) score, this score has a minimal clinically important difference (MCID) of 5 points[25], which was not seen in the study. Subgroup analysis suggests a possible benefit in patients with LVEF less than or equal to 57% (RR 0.78, 95% CI 0.64-0.95) compared to those with higher baseline LVEF (RR 1.00, 95% CI 0.81-1.23). The FDA reviewers note that benefits are clearly more evident in patients with LVEF below normal and clinical judgement should be used in deciding who to treat. There was also a more pronounced benefit seen in women (RR 0.73; 95% CI 0.59-0.90) compared to men (RR 1.03; 95% CI 0.85- 1.25). Slightly over half (52%) of participants were female. Reasons for this difference are not entirely clear but could be due to several considerations. The normal LVEF range is higher in women than in men; however, women have more evidence of contractile dysfunction for a given EF.[26] Since sacubitril/valsartan is more effective in patients with left ventricular systolic dysfunction, women may benefit more. Other differences that may contribute to a difference is more pronounced age-related arterial stiffening in women and sex differences in natriuretic peptide biology.[26]

Table 4: Evidence table for sacubitril/valsartan in heart failure with HFpEF

Ref./ Study Design	**Drug Regimens/ Duration**	**Patient Population**	**N**	**Efficacy Endpoints** N (%) RR,HR (95% CI)	**ARR/NNT**	**Safety Outcomes** N (%) P value	**ARI/NNH**	**Quality Rating Risk of Bias/Applicability**
Paragon-HF[1] MC, R, AC, DB	1. Sacubitril/Valsartan 97/103 BID (ARNI) 2. Valsartan 160 BID (ARB)	Demographics: Age: 72 years Females: 51% White: 81% Asian:12.5% Black: 2%	ITT ARNI: 2407 ARB: 2389	Primary Endpoint: HF Hospitalizations and CV death: ARNI: 894 (37.1%) ARB: 1009 (42.2%)		Discontinuations due to AE: ARNI: 370 (15.4%) ARB: 387 (16.2%) *p-value not reported	NA	**Risk of Bias** (low/high/unclear): Selection bias: Low; blinding with computer generated sequence using interactive response technology, baseline characteristics similar.

	Study Phases -ARB run-in (15 days IQR 12-22 days) -ARNI run-in (19 days IQR 15-23 days) -1:1 Randomization to either ARNI or ARB	NYHA Class I: 3% NYHA Class II: 77% NYHA Class III: 19% NYHA Class IV: 0% LVEF: 57.5% ±8% Ischemic cause: 36% BB: 79.5% Diuretic: 95% ACE/ARB: 86% MCRA: 26% Key Inclusion Criteria: Age>= 50 NYHA class II to IV LVEF >= 45% Evidence of structural HD On diuretic therapy Key Exclusion Criteria: Any prior LVEF < 40% SBP < 110 Acute decompensated HF eGFR < 30 K+ > 5.2 ACS Coronary or carotid artery disease likely require surgery Life expectancy < 3 years	Attrition ARNI: 370 (15.4%) ARB: 387 (16.2%)	RR 0.87 (0.75 to 1.01) Secondary Endpoints: Death from any cause ARNI: 342 (14.2%) ARB: 349 (14.6%) HR 0.97; 95% CI 0.84-1.13 Change in KCCQ score MCID for KCCQ: 5 points ARNI: -1.6 points +/- 0.4 ARB: -2.6 points +/-0.4 RD 1.0 (Range: 0.0-2.1) Renal composite outcome* ARNI: 33 (1.4%) ARB: 64 (2.7%) HR 0.50; 95% CI 0.33-0.77 *death from renal failure, end-stage renal disease, or decrease in eGFR >50% from baseline	NS NS NA 1.3% / NNT 77	Hypotension ARNI: 380 (15.8%) ARB: 257 (10.8%) p<0.001 Angioedema ARNI: 14 (0.6%) ARB: 4 (0.2%) P=0.02	ARI 5%/ NNH 20 ARI 0.4%/ NNH 250	Performance bias: unclear; blinding of participants and investigators, double dummy design. However, run-in period increases the risk of unblinding. Detection bias: low; outcome assessors and data analysts blinded Attrition bias: Low; <1% dropout in both groups, however dropout occurred prior to randomization (9.4% dropout, n=541, in valsartan run-in phase, 7.4% dropout, n=384, in ARNI run-in phase.) Publication bias: Low; study protocol available, prespecified outcomes of interest reported **Applicability**: Patient: Run-in period excluded higher risk patients and those at higher risk for adverse events. Since patients with HFpEF have lower circulating neprilysin levels, a neprilysin inhibitor may be less effective. Lacked racial diversity. Intervention: maintenance dose of ARNI designed to yield systemic exposure of valsartan equivalent to 320 mg/day. 82% in ARNI group achieved target dose vs. 85% in ARB group. Comparator: valsartan may have potential beneficial effect in HFpEF and impacted lower than expected treatment difference. Outcomes: clinically relevant outcomes with composite endpoint driven more by decreased morbidity. Used total hospitalizations, including recurrent, instead of more common time to first-event analysis. Setting: Multicenter study with 12% in North America.

Abbreviations [alphabetical order]: AC = Active control; ACS = Acute coronary syndrome; AE = adverse events; ARB = Angiotensin receptor blocker; ARI = absolute risk increase; ARNI: Angiotensin receptor neprolysin inhibitor; ARR = absolute risk reduction; BB = beta blocker; BID = Twice per day; CI = confidence interval; CV = Cardiovascular; DB = Double Blind; eGFR = estimated glomerular filtration rate; HD = Heart Disease; HF = Heart Failure; HR = hazard ratio; IQR = Interquartile range; ITT = intention to treat; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; MC = Multi-Center; MCID = Minimum Clinically Important difference; MCRA = Mineralocorticoid Receptor antagonist; MD = mean difference; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NYHA = New York Heart Association; OR = Odds Ratio; PP = per protocol; R = Randomized; RD = Risk Difference; RR = relative risk; SAE = serious adverse events; SBP = Systolic Blood Pressure; SCr = Serum Creatinine;

Randomized Controlled Trials:
A total of 9 citations were manually reviewed from the initial literature search. After further review, 8 citations were excluded because of wrong study design[27-30] (e.g., post-hoc analysis, observational), comparator[31] (e.g., no control or placebo-controlled), study population[32] (e.g. acute MI) or outcome studied[33-35] (e.g., non-clinical). The trial supporting the new indication is included in the previous evidence table (**Table 4)** and the remaining trial is summarized in the table below (**Table 5**). Full abstracts are included in **Appendix 2**.

Table 5. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	
McMurry et al.[26] Prespecified subgroup analysis of PARAGON-HF trial	Sacubitril/valsartan (ARNI) 97/103 mg BID vs. valsartan (ARB) 160 mg BID	HFrEF (LVEF > 45%), structural heart disease, and elevated NP level	Composite of first and recurrent hospitalizations for heart failure and death from CV cause	<u>Women</u> ARNI: 391 (32%) ARB: 532 (43%) RR 0.73; 95% CI 0.60-0.90	<u>Men</u> ARNI: 503 (43%) ARB: 477 (41%) RR 1.02; 95% CI 0.83-1.24
Abbreviations: ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; BID: twice daily; CI = confidence interval; CV: cardiovascular; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction; NP: natriuretic peptide; RR: rate ratio					

<u>NEW DRUG EVALUATION:</u>

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Vericiguat is a soluble guanylate cyclase (sGC) stimulator, indicated to reduce the risk of CV death and HF hospitalization following a hospitalization for heart failure or need for outpatient intravenous (IV) diuretics, in adults with symptomatic chronic HF and ejection fraction less than 45%.[36] Soluble guanylate cyclase stimulates production of cyclic guanosine monophosphate (cGMP), a signaling molecule involved in vascular smooth muscle relaxation, cardiac contractility, and cardiac remodeling. It is proposed that vericiguat works through the nitric oxide pathway to increase intracellular cGMP, thus improving myocardial and vascular function via vasodilation and reduction of cardiac afterload. Through a different pathway than sacubitril/valsartan, it also augments natriuretic peptides.

Vericiguat demonstrated no benefit in reducing the level of N-terminal pro-B natriuretic peptide (NT-pro BNP) in an earlier phase 2 study in stable HF.[37] Therefore, this study was designed to include patients with advanced symptomatic heart failure who had recently been hospitalized or received IV diuretics (recent decompensated) with higher baseline NT-pro BNP levels.

Clinical Efficacy:
Approval was based on one placebo-controlled, multi-center, double-blind RCT (VICTORIA) comparing vericiguat to placebo in adults with HFrEF (ejection fraction <45%), NYHA Class II-IV, and an elevated natriuretic peptide level following a worsening HF event (**Table 7**).[3] A worsening HF event was defined as HF hospitalization within the previous 6 months or use of IV diuretics within 3 months before randomization. This was a higher risk population with 41% of patients with NYHA Class III or IV and a baseline NT-proBNP of 2816 pg/ml. Most participants had a HF hospitalization within the last 3 months (67%). The median follow-up period was 10.8 months. Sixty percent of patients were on background therapy with a beta-blocker, mineralocorticoid antagonist, and a renin-angiotensin system inhibitor (ACE-I, ARB, or ARNI). Additionally, 93% of patients were on a beta-blocker, 73% were on an ACE-I or ARB, and 70% were on a mineralocorticoid antagonist. Patients in the vericiguat group were started on 2.5 mg once daily and titrated up to a target dose of 10 mg once daily. Dose modification were based on systolic blood pressure and symptomatic hypotension. After 12 months, 89.2% in the vericiguat group were receiving the 10 mg target dose.[37]

The primary outcome was first occurrence of the composite of CV death or HF hospitalization. There was a statistically significant reduction in the primary outcome at a median of 10.8 months with vericiguat compared to placebo (35.5% vs. 38.5%; HR 0.90; 95% CI 0.82 to 0.98; NNT 34) that was driven by HF hospitalizations. There was a non-significant reduction in death from CV causes and no significant difference in all-cause mortality (**Table 7**).

There did not appear to be differences in subgroups of gender, race, or geographic region. However, pre-specified subgroup analysis did not show a benefit in the subjects in the highest quartile of NT-proBNP at baseline (> 5314 pg/mL), but instead showed a higher rate of CV death in the vericiguat group compared to placebo (208 [34%] vs. 169 [29%]), driven by sudden cardiac death.[37] There was also no significant benefit in the primary outcome in the subgroup of participants age 75 or older (HR 1.04; 95% CI 0.88 – 1.21). Post hoc analysis identified a significant interaction for the outcome of CV death by the presence (HR 0.69; 95% CI 0.55-0.88) or absence. (HR 1.06; 95% CI 0.90-1.25) of an implantable cardioverter defibrillator (ICD) at baseline, suggesting that devices are protective.[37] The unfavorable trend in CV death was most notable among those in the highest baseline NT-proBNP quartile without a device at baseline (HR 1.38; 95% CI 1.08-1.75).[37] Based on these findings, the FDA did a focused search and concluded that vericiguat is not proarrhythmic but included the observations in the labeling.

Risk of bias was generally low in the study. There was a high rate of overall discontinuation in both groups, but an intention-to-treat analysis was used to evaluate the primary outcome. Generalizability and applicability to clinical practice is low based on the narrow patient population and many exclusion criteria. Sites in the United States contributed 8% of subject enrollment. With challenges in adherence with complex medication regimens and increasing costs, emphasis should be put on optimizing goal directed medications, including beta-blockers and inhibitors of the renin-angiotensin system. Only 15% of subjects were on sacubitril/valsartan and it is remains unknown if the combination would be synergistic or would increase adverse events including hypotension and syncope. Vericiguat should not be used in patients with HFpEF, as a 6-month placebo-controlled study resulted in a higher rate of CV death with vericiguat compared to placebo (3.8% vs. 1.5%) and no improvement in the physical limitation score of the KCCQ.[37,38]

Clinical Safety:
Serious adverse events occurred in 32.8% of the patients in the vericiguat group and in 34.8% of the patients in the placebo group. The most common side effects that occurred more commonly with vericiguat than placebo included hypotension (16% vs. 15%) and anemia (10% vs. 7%).[36] Symptomatic hypotension occurred in 9.1% of the patients in the vericiguat group and in 7.9% of the patients in the placebo group (P=0.12), and syncope occurred in 4.0% of patients in the vericiguat group and in 3.5% of patients in the placebo group (P=0.30). Symptomatic hypotension and syncope are side effects of concern due to the vasodilatory mechanism of action of vericiguat. The FDA reviewers noted that they were not associated with serious events such as increased falls or fractures and anemia did

not result in clinical bleeding.[24] Vericiguat may cause fetal harm and is contraindicated in pregnancy. Inclusion criteria included male or female confirmed to be postmenopausal, without childbearing potential or use of acceptable contraception.

Comparative Endpoints:

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 6. Pharmacology and Pharmacokinetic Properties.[36]

Parameter	
Mechanism of Action	Vericiguat is a stimulator of soluble guanylate cyclase (sGC), an important enzyme in the nitric oxide (NO) signaling pathway. This catalyzes the synthesis of intracellular cyclic guanosine monophosphate (cGMP), a second messenger that plays a role in the regulation of vascular tone, cardiac contractility, and cardiac remodeling.
Oral Bioavailability	93%
Distribution and Protein Binding	44L; protein binding is about 98%
Elimination	Approximately 53% of the dose was excreted in urine (primarily as inactive metabolite) and 45% in feces (primarily as unchanged drug)
Half-Life	30 hours
Metabolism	Primarily undergoes glucuronidation by UGT1A9 and to a lesser extent, by UGT1A1 to form an inactive N-glucuronide metabolite. CYP-mediated metabolism is a minor clearance pathway (<5%).

Table 7. Comparative Evidence Table.

Ref./ Study Design	**Drug Regimens/ Duration**	**Patient Population**	**N**	**Efficacy Endpoints** N (%) RR,RD (95% CI)	**ARR/NNT**	**Safety Outcomes** N (%) P value	**ARR/NNH**	**Quality Rating Risk of Bias/Applicability**
Victoria[3] MC, PC, DB, RCT	1. Vericiguat 10 mg daily 2. Placebo On background guideline-based medical therapy	Demographics: Age: 67 years Females: 23.9% White: 64% Mean LVEF 29% NYHA II: 59% NYHA III: 40% NYHA IV:1.3%	ITT 1. 2526 2. 2524 Attrition 1. 610 (24%)	Primary Endpoint: HF Hospitalizations and CV death: 1. 897 (35.5%) 2. 972 (38.5%) HR 0.90; 95% CI 0.82-0.98 P=0.02	ARR 3%/ NNT 34	Discontinuations due to AE: 1. 177 (7%) 2. 159 (6.3%) Symptomatic Hypotension 1. 229 (9.1%)	NA NS	**Risk of Bias** (low/high/unclear): Selection bias: low; treatment allocation and randomization using an interactive voice response system, baseline characteristics well balanced between groups. Performance bias: low; double blinded using double dummy approach

	X 12 months	<u>Key Inclusion Criteria</u>: ○ Age>= 18 ○ NYHA class II to IV ○ HF hospitalization within 6 months or IV diuretic within 3 months ○ Elevated BNP or NT-proBNP ○ LVEF < 45% <u>Key Exclusion Criteria</u>: ○ SBP < 110 ○ Use of LA nitrates, NO donors and PDE5 inhibitors ○ ACS within 60 days ○ eGFR < 15 ml/min ○ Severe hepatic insufficiency ○ Current alcohol or drug abuse	2. 565 (22%)	<u>Death from CV cause</u> 1. 414 (16.4%) 2. 441 (17.5%) HR 0.93; 95% CI 0.81-1.06 <u>Death from any cause</u> 1. 512 (20.3%) 2. 534 (21.2%) HR 0.95; 95% CI 0.84-1.07	 NS NS	2. 198 (7.9%) P=0.12		<u>Detection bias</u>: low; Members of an independent clinical-events committee who were unaware of the trial-group assignments adjudicated all deaths and hospitalizations <u>Attrition bias</u>: unclear; high overall attrition but similar in each group and ITT analysis done for the primary outcome. Data on patients who withdrew were censored at the last available follow-up time. <u>Publication bias:</u> low; study protocol available, prespecified outcomes of interest reported **Applicability**: <u>Patient</u>: Narrow inclusion and exclusion criteria limits generalizability to patients with advanced symptomatic heart failure on guideline directed therapy. <u>Intervention</u>: Unclear if strong dose response based on Phase 2 data <u>Comparator</u>: placebo appropriate comparator based on potential place in therapy <u>Outcomes</u>: clinically relevant outcomes with composite endpoint driven more by decreased hospitalizations <u>Setting</u>: 694 sites in 42 countries. 11% from North America (8% from US), 14% Latin America, 23% Asia, 17% western Europe, 33.5% eastern Europe

<u>Abbreviations</u> [alphabetical order]: ACS = Acute coronary syndrome; AE = adverse event; ARR = absolute risk reduction; BID = Twice per day; BNP = brain natriuretic peptide; CI = confidence interval; CV = Cardiovascular; DB = Double-Blind; GFR = glomerular filtration rate; HD = Heart Disease; HF = Heart Failure; HR = hazard ratio; ITT = intention to treat; KCCQ = Kansas City Cardiomyopathy Questionnaire; LA = long acting; LVEF = left ventricular ejection fraction; MC = Multi-Center; MD = mean difference; N = number of subjects; NA = not applicable; NO = nitric oxide; NNH = number needed to harm; NNT = number needed to treat; NT-proBNP = N-terminal pro BNP; NYHA = New York Heart Association; OR = Odds Ratio; PC = placebo controlled; PDE5 inhibitor = phosphodiesterase 5 inhibitor; PP = per protocol; RCT = Randomized; RD = Risk Difference; RR = relative risk; SAE = serious adverse events; SBP = Systolic Blood Pressure

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Appendix 1: Current Preferred Drug List

ACEIs, ARBs, DRIs, and Sacubatril/Valsartan

Generic	Brand	Route	Form	PDL
benazepril HCl	BENAZEPRIL HCL	ORAL	TABLET	Y
benazepril HCl	LOTENSIN	ORAL	TABLET	Y
enalapril maleate	ENALAPRIL MALEATE	ORAL	TABLET	Y
enalapril maleate	VASOTEC	ORAL	TABLET	Y
irbesartan	AVAPRO	ORAL	TABLET	Y
irbesartan	IRBESARTAN	ORAL	TABLET	Y
lisinopril	LISINOPRIL	ORAL	TABLET	Y
lisinopril	PRINIVIL	ORAL	TABLET	Y
lisinopril	ZESTRIL	ORAL	TABLET	Y
losartan potassium	COZAAR	ORAL	TABLET	Y
losartan potassium	LOSARTAN POTASSIUM	ORAL	TABLET	Y
olmesartan	BENICAR	ORAL	TABLET	Y
olmesartan	OLMESARTAN MEDOXOMIL	ORAL	TABLET	Y
ramipril	ALTACE	ORAL	CAPSULE	Y
ramipril	RAMIPRIL	ORAL	CAPSULE	Y
telmisartan	MICARDIS	ORAL	TABLET	Y
telmisartan	TELMISARTAN	ORAL	TABLET	Y
valsartan	DIOVAN	ORAL	TABLET	Y
valsartan	VALSARTAN	ORAL	TABLET	Y
aliskiren	ALISKIREN	ORAL	TABLET	N
aliskiren	TEKTURNA	ORAL	TABLET	N
azilsartan medoxomil	EDARBI	ORAL	TABLET	N
candesartan cilexetil	ATACAND	ORAL	TABLET	N
candesartan cilexetil	CANDESARTAN CILEXETIL	ORAL	TABLET	N
captopril	CAPTOPRIL	ORAL	TABLET	N
enalapril maleate	EPANED	ORAL	SOLUTION	N
eprosartan mesylate	TEVETEN	ORAL	TABLET	N
fosinopril sodium	FOSINOPRIL SODIUM	ORAL	TABLET	N
lisinopril	QBRELIS	ORAL	SOLUTION	N
moexipril HCl	MOEXIPRIL HCL	ORAL	TABLET	N

perindopril erbumine	PERINDOPRIL ERBUMINE	ORAL	TABLET	N
quinapril HCl	ACCUPRIL	ORAL	TABLET	N
quinapril HCl	QUINAPRIL HCL	ORAL	TABLET	N
trandolapril	TRANDOLAPRIL	ORAL	TABLET	N
sacubitril/valsartan	ENTRESTO	ORAL	TABLET	

Unassigned in Preferred Drug List (STC class 72 – Vasodilators: Coronary)

Generic	Brand	Route	Form	PDL
vericiguat	VERQUVO	PO	TABLET	

Appendix 2: Abstracts of Comparative Clinical Trials

- John J V McMurray, Alice M Jackson, Carolyn S P Lam, Margaret M Redfield, et al. Effects of Sacubitril-Valsartan Versus Valsartan in Women Compared With Men With Heart Failure and Preserved Ejection Fraction: Insights From PARAGON-HF. *Circulation.* 2020 Feb 4;141(5):338-351. Epub 2019 Nov 17.

  Background: Unlike heart failure with reduced ejection fraction, there is no approved treatment for heart failure with preserved ejection fraction, the predominant phenotype in women. Therefore, there is a greater heart failure therapeutic deficit in women compared with men.

  Methods: In a prespecified subgroup analysis, we examined outcomes according to sex in the PARAGON-HF trial (Prospective Comparison of ARNI With ARB Global Outcomes in Heart Failure With Preserved Ejection Fraction), which compared sacubitril-valsartan and valsartan in patients with heart failure with preserved ejection fraction. The primary outcome was a composite of first and recurrent hospitalizations for heart failure and death from cardiovascular causes. We also report secondary efficacy and safety outcomes.

  Results: Overall, 2479 women (51.7%) and 2317 men (48.3%) were randomized. Women were older and had more obesity, less coronary disease, and lower estimated glomerular filtration rate and NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels than men. For the primary outcome, the rate ratio for sacubitril-valsartan versus valsartan was 0.73 (95% CI, 0.59-0.90) in women and 1.03 (95% CI, 0.84-1.25) in men (P interaction = 0.017). The benefit from sacubitril-valsartan was attributable to reduction in heart failure hospitalization. The improvement in New York Heart Association class and renal function with sacubitril-valsartan was similar in women and men, whereas the improvement in Kansas City Cardiomyopathy Questionnaire clinical summary score was less in women than in men. The difference in adverse events between sacubitril-valsartan and valsartan was similar in women and men.

  Conclusions: As compared with valsartan, sacubitril-valsartan seemed to reduce the risk of heart failure hospitalization more in women than in men. Whereas the possible sex-related modification of the effect of treatment has several potential explanations, the present study does not provide a definite mechanistic basis for this finding.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to April 09, 2021>

1	entresto.mp.	78
2	sacubitril.mp.	1159
3	Valsartan/	2363
4	heart failure.mp. or Heart Failure/	218026
5	cardiovascular outcomes.mp.	8844
6	Mortality/de [Drug Effects]	2
7	cardiovascular mortality.mp.	14354
8	Myocardial Infarction/ or major adverse cardiovascular events.mp. or Coronary Artery Disease/	229672
9	hospitalization.mp. or Hospitalization/	216868
10	quality of life.mp. or "Quality of Life"/	369617
11	2 and 3	202
12	1 or 11	272
13	5 or 6 or 7 or 8 or 9 or 10	814172
14	4 and 12	212
15	13 and 14	54
16	limit 15 to (yr="2017 -Current" and english and (clinical trial, phase iii or clinical trial, phase iv or comparative study or meta analysis or randomized controlled trial or "systematic review"))	12

Appendix 4: Prescribing Information Highlights

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

VERQUVO™ (vericiguat) tablets, for oral use
Initial U.S. Approval: 2021

WARNING: EMBRYO-FETAL TOXICITY
See full prescribing information for complete boxed warning.
- **Do not administer VERQUVO to a pregnant female because it may cause fetal harm. (4, 5.1, 8.1)**
- **Females of reproductive potential: Exclude pregnancy before the start of treatment. To prevent pregnancy, females of reproductive potential must use effective forms of contraception during treatment and for one month after stopping treatment. (2.2, 5.1, 8.3)**

----------INDICATIONS AND USAGE----------
VERQUVO is a soluble guanylate cyclase (sGC) stimulator, indicated to reduce the risk of cardiovascular death and heart failure (HF) hospitalization following a hospitalization for heart failure or need for outpatient IV diuretics, in adults with symptomatic chronic HF and ejection fraction less than 45%. (1)

---------- DOSAGE AND ADMINISTRATION ----------
- The recommended starting dose of VERQUVO is 2.5 mg orally once daily with food. (2.1)
- Double the dose of VERQUVO approximately every 2 weeks to reach the target maintenance dose of 10 mg once daily, as tolerated by the patient. (2.1)
- Tablets may be crushed and mixed with water for patients who have difficulty swallowing. (2.1)

---------- DOSAGE FORMS AND STRENGTHS ----------
Tablets: 2.5 mg, 5 mg and 10 mg (3)

----------CONTRAINDICATIONS----------
- Patients with concomitant use of other soluble guanylate cyclase (sGC) stimulators. (4, 7.1)
- Pregnancy (4)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions reported in ≥5% are hypotension and anemia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- PDE-5 Inhibitors: Concomitant use is not recommended. (7.2)

---------- USE IN SPECIFIC POPULATIONS ----------
- Lactation: Breastfeeding is not recommended (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 01/2021

Appendix 5: Key Inclusion Criteria

Population	**Chronic heart failure**
Intervention	Sacubitril/valsartan or vericiguat
Comparator	ACE inhibitor or angiotensin aldosterone receptor antagonist or placebo
Outcomes	Heart failure hospitalization, cardiovascular mortality, all-cause mortality, symptomatic improvement, quality of life
Timing	N/A
Setting	Inpatient hospital or outpatient clinic

Appendix 6: Prior Authorization Criteria

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:

- 3 to 12 months

Requires PA:

Sacubitril/valsartan (Entresto™)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is this a request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to Renewal Criteria	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code. Go to #3	
3. Does the patient have chronic heart failure (New York Heart Association [NYHA] Class II-IV)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the patient 17 years of age or younger?	**Yes:** Go to #5	**No:** Go to # 7
5. Does the patient have left ventricular systolic dysfunction (ejection fraction less than 40% (LVEF ≤ 40%)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the medication prescribed by or in consultation by a cardiologist or heart failure provider?	**Yes:** Approve for 3 months	**No:** Pass to RPh. Deny, medical appropriateness

Approval Criteria		
7. Has the patient tolerated a minimum daily dose an ACE-inhibitor or ARB listed in Table 1 for at least 30 days? *Note: ACE inhibitors must be discontinued at least 36 hours prior to initiation of sacubitril/valsartan*	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Does the patient have heart failure with reduced ejection fraction less than 40% (LVEF ≤ 40%)?	**Yes:** Go to #9	**No:** Approve for 3 months *Note: Benefits of therapy are most clearly evident in patients with left ventricular ejection fraction below normal. Use judiciously with higher baseline ejection fraction*
9. 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 heart failure guidelines.[1,2] Carvedilol and metoprolol succinate are preferred agents on the PDL.*	**Yes:** Go to #10	**No:** Pass to RPh. Deny, medical appropriateness
10. Is there evidence of adherence and tolerance to goal directed heart failure therapy (beta-blocker and ACE-I/ARB) through pharmacy claims/refill history and provider assessment?	**Yes:** Approve for 3 months	**No:** Pass to RPh. Deny, medical appropriateness

Renewal Criteria		
1. Is the patient 18 years or older or at least 50 kg?	**Yes:** Go to #2	**No:** Go to #3
2. Is the patient currently taking sacubitril/valsartan at the target dose of 97/103 mg 2-times daily to a maximum dose as tolerated by the patient?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh and go to #4

Renewal Criteria		
3. Is the patient currently taking sacubitril/valsartan at the target dose in Table 2 or to a maximum dose as tolerated by the patient?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh and go to #4
4. What is the clinical reason the drug has not been titrated to the target dose?	Document rationale and approve for up to 90 days. Prior authorization required every 90 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	100 mg/day	Candesartan	16 mg/day
Enalapril	10 mg/day	Losartan	50 mg/day
Lisinopril	10 mg/day	Valsartan	160 mg/day
Ramipril	5 mg/day	Olmesartan	10 mg/day
Trandolapril	2 mg/day	Irbesartan	150 mg/day
Fosinopril	20 mg/day		

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 to improve chances of tolerability to the target maintenance dose of sacubitril/valsartan 97/103 mg 2-times daily.[3]
- Valsartan formulated in sacubitril valsartan 97/103 mg 2-times daily is bioequivalent to valsartan 160 mg 2-times daily.[4]
- 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]

Table 2: Target dose of sacubitril/valsartan in pediatric heart failure[4]

Population	Target Dose
Patients less than 40 kg	3.1 mg/kg twice daily
Patients at least 40 kg, less than 50 kg	72/78 mg twice daily
Patients at least 50 kg	97/103 mg twice daily

References:

1. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2017;136(6):e137-e161.
2. McMurray J, Adamopoulos S, Anker S, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. European Journal of Heart Failure. 2012;14:803-869. doi:10.1093/eurjhf/hfs105.
3. McMurray J, Packer M, Desai A, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Eng J Med*. 2014;371:993-1004. doi:10.1056/NEJMoa1409077.
4. ENTRESTO (sacubitril and valsartan) [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals, February 2021.

P&T / DUR Review: *6/21(MH); 05/17(DM), 09/15*
Implementation: *7/1/21; 10/13/16; 10/1/15*

Author: Herink Date: June 2021

Vericiguat (Verquvo®)

Goal(s):

- Restrict use of vericiguat in populations and at doses in which the drug has demonstrated efficacy.
- Encourage use of beta-blockers and inhibitors of the renin-angiotensin-aldosterone system with demonstrated evidence of mortality reduction in heart failure with reduced ejection fraction.

Length of Authorization:

- 6 to 12 months

Requires PA:

Vericiguat (Verquvo®)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is this a request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to Renewal Criteria	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code. Go to #3.	
3. Does the patient have symptomatic New York Heart Association (NYHA) Class II to IV chronic heart failure?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Does the patient have reduced ejection fraction (< 45%) assessed within the previous 12 months?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Does the patient have worsening heart failure defined as one of the following? a. History of previous heart failure hospitalization within the last 6 months b. Intravenous diuretic use within previous 3 months	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
6. Is the patient currently being seen by a cardiologist or heart failure specialist for management of advanced disease?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the patient on an angiotensin system inhibitor at maximally tolerated dose, such as: a. Angiotensin converting enzyme inhibitor (ACE-I) b. Angiotensin receptor blocker (ARB) c. Angiotensin receptor-neprilysin inhibitor (ARNI)	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. 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:** Go to #9	**No:** Pass to RPh. Deny, medical appropriateness
9. Is there evidence of adherence and tolerance to goal directed heart failure therapy (beta-blocker and angiotensin inhibitor) through pharmacy claims/refill history and provider assessment?	**Yes:** Go to #10	**No:** Pass to RPh. Deny, medical appropriateness
10. Is the patient on long-acting nitrates such as isosorbide dinitrate, isosorbide 5-mononitrate, transdermal nitroglycerin, or other similar agents or phosphodiesterase-5 (PDE5) inhibitors (e.g. sildenafil, tadalafil)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #11
11. Does the patient have stage 5 chronic kidney disease (eGFR < 15 ml/min or on hemodialysis/peritoneal dialysis)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #12
12. Is the patient of childbearing potential?	**Yes:** Go to #13	**No:** Approve for 6 months

Approval Criteria		
13. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #14
14. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny, medical appropriateness

Renewal Criteria		
1. Has the patient developed symptomatic hypotension or syncope while on vericiguat?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #2
2. Has the patient experienced disease progression, defined as either worsening NYHA functional class or worsening signs and symptoms of heart failure requiring intensification of therapy?	**Yes:** Go to #3	**No:** Approve for 12 months
3. Is the patient currently being seen by a cardiologist or heart failure specialist for management of advanced disease?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

References:
1. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62(16):e147-239. doi: 10.1016/j.jacc.2013.05.019.
2. McMurray J, Adamopoulos S, Anker S, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. European Journal of Heart Failure. 2012;14:803-869. doi:10.1093/eurjhf/hfs105.

P&T / DUR Review: *06/21 (MH)*
Implementation: *7/1/21*