

New Drug Overview Entresto® (sacubitril/valsartan)

Overview/Summary: Entresto® (sacubitril/valsartan) is a novel combination therapy containing sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin II receptor blocker (ARB). This agent is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure (HF) in patients with chronic heart failure (New York Heart Association [NYHA] Class II to IV) and reduced ejection fraction (EF). This medication provides complementary cardiovascular benefits as well as renal effects through two distinct mechanisms. First, sacubitril inhibits neprilysin via LBQ657, the active metabolite of the prodrug sacubitril. This neprilysin inhibition reduces the degradation of natriuretic peptides which are important for promoting vasodilation, natriuresis, diuresis, inhibition of renin and aldosterone release as well as anti-hypertrophic and anti-fibrotic effects. The second mechanism of action of this agent includes preventing the effects of angiotensin II by selectively blocking the AT₁ receptor with valsartan.^{1,2}

Sacubitril/valsartan was reviewed under the FDA's priority review program, which provides for expedited review of drugs that are intended to treat a serious disease or condition and may provide a significant improvement over available therapy. It was also granted fast track designation, which supports the FDA's efforts to facilitate the development and expedite the review of drugs to treat serious or life-threatening conditions and fill an unmet medical need.³

Table 1. Dosing and Administration¹

Generic Name	Adult Dose	Pediatric Dose	Availability
Sacubitril/valsartan	<p><u>Patients with chronic heart failure (NYHA Class II to IV) and reduced ejection fraction:</u> Tablet: initial, 49/51 mg BID; maintenance and maximum, 97/103 mg BID</p> <p><u>Dosage for patients NOT previously taking an ACEI or ARB or previously taking low doses of these agents:</u> Tablet: initial, 24/26 mg BID; maintenance and maximum, 97/103 mg BID</p>	Safety and efficacy in children have not been established.	Tablet: 24/26 mg 49/51 mg 97/103 mg

Evidence-based Medicine

- The safety and efficacy of Entresto® (sacubitril/valsartan) was established in a randomized, double-blind trial in patients with chronic heart failure (NYHA class II to IV) and left ventricular EF ≤ 40%, which was later changed to ≤ 35%) stabilized on an ACEI or ARB for at least four weeks and on maximally tolerated doses of β-blockers (N=8,442).⁵
 - Sacubitril/valsartan was associated with a greater risk reduction for the composite of death from cardiovascular causes or hospitalization for heart failure compared to enalapril (21.8% compared with 26.5%; hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.73 to 0.87; P<0.0001).
 - The treatment effect reflected a reduction in cardiovascular death (13.3% in the sacubitril/valsartan group and 16.5% in the enalapril group) and HF hospitalization (12.8% of patients in the sacubitril/valsartan group and 15.6% of patients in the enalapril group).
 - Sacubitril/valsartan was associated with a reduction in all-cause mortality compared to enalapril (711 [17.0%] vs 835 [19.8%]; HR, 0.84; 95% CI, 0.76 to 0.93; P<0.0001).

Key Points within the Medication Class

- According to Current Clinical Guidelines:
 - The 2013 guidelines from the American College of Cardiology Foundation/American Heart Association continue to recommend that all individuals with hypertension and lipid disorders should be controlled according to contemporary guidelines to lower the risk of HF.⁴
 - § Specifically in Stage B-D HF with reduced ejection fraction, individuals should be given an angiotensin converting enzyme inhibitor (ACEI) to prevent symptomatic HF and reduce mortality. An ARB is recommended if the patient cannot tolerate an ACEI.
 - § In patients with a recent or remote history of myocardial infarction (MI) or acute coronary syndrome (ACS) and reduced EF, a β -blocker such as bisoprolol, carvedilol or sustained-release metoprolol succinate, is recommended for all patients.
 - § In the case of volume overload, in NYHA class II to IV patients, it is recommended to add a diuretic, unless contraindicated, to improve symptoms. The loop diuretics are currently the preferred diuretics.
 - § Aldosterone receptor antagonists are also recommended to reduce morbidity and mortality following an acute MI in patients with a left ventricular ejection fraction (LVEF) \leq 40% who develop symptoms of HF or who have a history of diabetes mellitus, unless contraindicated.
 - Consensus guidelines in the U.S. have not been updated to address this medication's place in therapy.
- Other Key Facts:
 - This agent is associated with a significant toxicity profile including: angioedema, hypotension, hyperkalemia and a risk of teratogenicity.¹
 - The effect of this agent in individuals with heart failure with preserved ejection fraction (HFpEF) is currently unknown.

References

1. Entresto[®] [package insert]. East Hanover (NJ): Novartis 2015 July.
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4. Yancy CW, Jessup M, Bozhurt B, Butler J, Casey DE, Drazner MH, et al. 2013 ACCF/AHA Guideline for the management of heart failure. *Circulation*. 2013;128:e240-e327.
5. McMurray JJ, Packer M, Desai A, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014 Sep 11;371(11):993-1004.

New Drug Review **Entresto® (sacubitril/valsartan)**

Overview/Summary

Entresto® (sacubitril/valsartan) is a novel combination therapy containing sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin II receptor blocker (ARB). This agent is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure (HF) in patients with chronic heart failure (New York Heart Association [NYHA] Class II to IV) and reduced ejection fraction (EF). This medication provides complementary cardiovascular benefits as well as renal effects through two distinct mechanisms. First, sacubitril inhibits neprilysin via LBQ657, the active metabolite of the prodrug sacubitril. This neprilysin inhibition reduces the degradation of natriuretic peptides which are important for promoting vasodilation, natriuresis, diuresis, inhibition of renin and aldosterone release as well as anti-hypertrophic and anti-fibrotic effects. The second mechanism of action of this agent includes preventing the effects of angiotensin II by selectively blocking the AT₁ receptor with valsartan.^{1,2}

Sacubitril/valsartan was reviewed under the FDA's priority review program, which provides for expedited review of drugs that are intended to treat a serious disease or condition and may provide a significant improvement over available therapy. It was also granted fast track designation, which supports the FDA's efforts to facilitate the development and expedite the review of drugs to treat serious or life-threatening conditions and fill an unmet medical need.³

Indications

Sacubitril/valsartan is indicated to reduce the risk of cardiovascular death and hospitalization for HF in patients with chronic heart failure (NYHA Class II to IV) and reduced EF.

Pharmacokinetics

Table 1. Pharmacokinetics¹

Generic Name	Peak Concentration (hours)	Bioavailability (%)	Plasma Protein Binding (%)	Active Metabolites	Serum Half-Life (hours)
Sacubitril/valsartan	0.5 (sacubitril)/ 1.5 (valsartan)	≥60% (sacubitril)/ Not reported (valsartan)	94 to 97%	LBQ657	1.4 (sacubitril)/ 9.9 (valsartan)

Clinical Trials

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) was a multinational, randomized, double-blind trial in patients with symptomatic chronic heart failure (NYHA class II to IV) and systolic dysfunction (left ventricular EF ≤ 40% - later changed to ≤ 35%) stabilized on an ACEI or ARB for at least four weeks and on maximally tolerated doses of β-blockers (N=8,442). After discontinuing their existing ACEI/ARB therapy, patients entered sequential single-blind run-in periods during which they received enalapril 10 mg twice-daily for two weeks then held therapy with enalapril for one day, followed by sacubitril/valsartan 100 mg twice-daily, increasing to 200 mg twice daily for four to six weeks. Following these run-in periods, the sacubitril/valsartan was also held for one day prior to patients being randomized to sacubitril/valsartan 200 mg twice-daily or enalapril 10 mg twice daily. The primary endpoint was the first event in the composite of cardiovascular death or hospitalization for HF.⁵

Sacubitril/valsartan was associated with a greater risk reduction for the primary endpoint of composite of death from cardiovascular causes or hospitalization for heart failure compared to enalapril (914 patients [21.8%] vs 1,117 patients [26.5%]; hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.73 to 0.87; P <0.0001). The treatment effect reflected a reduction in cardiovascular death (558 patients in the sacubitril/valsartan group [13.3%] and 693 patients in the enalapril group [16.5%]) and HF hospitalization

(537 patients in the sacubitril/valsartan group [12.8%] vs 658 patients in the enalapril group [15.6%]). In addition, sacubitril/valsartan was associated with a reduction in all-cause mortality compared to enalapril (711 [17.0%] vs 835 [19.8%]; HR, 0.84; 95% CI, 0.76 to 0.93; P <0.0001).⁵ The study was stopped early when a highly statistically significant reduction in the risk of cardiovascular death was achieved in the sacubitril/valsartan group.

Table 2. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>McMurray et al.⁵ (PARADIGM-HF)</p> <p>Sacubitril/valsartan (LCZ696) 200 mg BID</p> <p>vs</p> <p>enalapril 10 mg BID</p> <p>After discontinuing their existing ACEI/ARB therapy, patients entered sequential single-blind run-in periods during which they received enalapril 10 mg twice-daily for two weeks then held therapy with enalapril for one day, followed by sacubitril/valsartan 100 mg twice-daily, increasing to 200 mg twice daily for four to six weeks before being randomized in final phase to sacubitril/valsartan or enalapril.</p>	<p>AC, DB, MC, RCT</p> <p>Patients with chronic HF (NYHA Class II to IV) symptoms, an LVEF of $\leq 40\%$ (changed to $\leq 35\%$ later in study) and a BNP ≥ 150 pg/mL (or N terminal proBNP ≥ 600 pg/mL), or, if hospitalized for HF within previous 12 months, a BNP of ≥ 100 pg/mL (or NT-proBNP ≥ 400 pg/mL), stable dose of a β-blocker (unless contraindicated or not tolerated), and a ACE-I or ARB equivalent to enalapril 10 mg daily for at least four weeks before screening along with a mineralocorticoid antagonist (if indicated)</p>	<p>N=8,399</p> <p>Median follow-up of 27 months (study terminated by data safety and monitoring board due to the boundary for an overwhelming benefit with sacubitril/valsartan had been reached)</p>	<p>Primary: Composite of death from cardiovascular causes or hospitalization for heart failure</p> <p>Secondary: Time to death from any cause, the change from baseline to eight months in the clinical summary score on the KCCQ, the time to new onset AF, time to first occurrence of decline in renal function</p>	<p>Primary: Sacubitril/valsartan was associated with a greater risk reduction of the combined cardiovascular endpoint compared to enalapril (914 [21.8%] vs 1,117 [26.5%]; HR, 0.80; 95% CI, 0.73 to 0.87; P <0.0001). The treatment effect reflected a reduction in cardiovascular death (558 patients in the sacubitril/valsartan group [13.3%] and 693 patients in the enalapril group [16.5%]) and HF hospitalization (537 patients in the sacubitril/valsartan group [12.8%] vs 658 patients in the enalapril group [15.6%]).</p> <p>Secondary: Sacubitril/valsartan was associated with a reduction in all-cause mortality compared to enalapril (711 [17.0%] vs 835 [19.8%]; HR, 0.84; 95% CI, 0.76 to 0.93; P <0.0001).</p> <p>The mean change from baseline to month eight in the KCCQ clinical summary score was a reduction in 2.99 points in the sacubitril/valsartan group and a reduction of 4.63 points in the enalapril group (between group difference, 1.64 points; 95% CI, 0.63 to 2.65; P=0.001).</p> <p>New onset atrial fibrillation was comparable for both groups (84 patients in the sacubitril/valsartan group and 83 in the enalapril group, P=0.84).</p> <p>Protocol-defined decline in renal function was seen in 94 patients in the sacubitril/valsartan group compared to 108 patients in the enalapril group (P=0.28).</p>

Drug regimen abbreviations: BID=twice daily

Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, HR=hazard ratio, MC=multicenter, RCT=randomized controlled trial

ACEI=angiotensin converting enzyme inhibitor, AF=atrial fibrillation, ARB=angiotensin receptor blocker, BNP= plasma B-type natriuretic peptide, CV=cardiovascular, ED=emergency department,

GMP=guanosine monophosphate, HF=heart failure, KCCQ=Kansas City Cardiomyopathy Questionnaire, LVEF=left ventricular ejection fraction, NYHA=New York Heart Association

Special Populations**Table 3. Special Populations¹**

Population	Precaution
Elderly	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.
Renal Dysfunction	No dose adjustment is required in patients with mild (eGFR 60 to 90 mL/min/1.73 m ²) to moderate (eGFR 30 to 60 mL/min/1.73 m ²) renal impairment. The recommended starting dose in patients with severe renal impairment (eGFR <30 mL/min/1.73 m ²) is 24/26 mg twice daily.
Hepatic Dysfunction	No dose adjustment is required when administering sacubitril/valsartan to patients with mild hepatic impairment (Child-Pugh A classification). The recommended starting dose in patients with moderate hepatic impairment (Child-Pugh B classification) is 24/26 mg twice daily. The use of this agent in patients with severe hepatic impairment (Child-Pugh C classification) is not recommended.*
Pregnancy/ Nursing	Sacubitril/valsartan can cause fetal harm when administered to a pregnant woman. When pregnancy is detected, consider alternative drug treatment and discontinue treatment. However, if there is no appropriate alternative to therapy with drugs affecting the renin angiotensin system, and if the drug is considered lifesaving for the mother, advise a pregnant woman of the potential risk to the fetus. There is no information regarding the presence of sacubitril/valsartan in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed infants from exposure to sacubitril/valsartan, advise a nursing woman that breastfeeding is not recommended during treatment.
Children	Safety and efficacy in children have not been established.*
Age Restrictions	FDA approved for use in patients ages ≥18 years of age.

*No adequate or well-controlled trials.

eGFR=estimate glomerular filtration rate

Adverse Drug Events

In the double-blind phase of PARADIGM-HF, safety was evaluated in 4,203 patients treated with sacubitril/valsartan and 4,229 treated with enalapril. Adverse reactions occurring at an incidence of ≥ 5% in patients who were treated with sacubitril/valsartan in the double-blind period are shown in Table 5.

In the double-blind period, the incidence of angioedema and orthostasis was higher in patients treated with sacubitril/valsartan than enalapril (0.5% vs 0.2% and 2.1% and 1.1%, respectively).¹

Table 4. Adverse Events Occurring at an Incidence of ≥ 5% in Patients Who Were Treated with sacubitril/valsartan¹

Adverse Event	Reported Frequency	
	Sacubitril/valsartan, %, N=4,203	Enalapril, %, N=4,229
Cough	9	13
Dizziness	6	5
Hyperkalemia	12	14
Hypotension	18	12
Dizziness	6	5
Renal failure/acute renal failure	5	5

Contraindications

Table 5. Contraindications¹

Contraindication	Sacubitril/valsartan
Hypersensitivity; sacubitril/valsartan should not be used in patients with known hypersensitivity.	a
Angioedema; sacubitril/valsartan should not be used in patients with a history of angioedema related to previous angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB).	a
Concomitant use with an ACEI; sacubitril/valsartan should not be used with an ACEI. Do not administer within 36 hours of switching from or to an ACEI.	a
Concomitant use with an aliskiren; sacubitril/valsartan should not be used with aliskiren in patients with diabetes.	a

Warnings/Precautions

Table 6. Warnings and Precautions¹

Warning/Precaution	Sacubitril/valsartan
Fetal Toxicity; sacubitril/valsartan can cause fetal harm when administered to a pregnant woman. Drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduce fetal renal function and increases fetal and neonatal morbidity and death. When pregnancy is detected, consider alternative drug treatment and discontinue treatment.	a
Hypotension; sacubitril/valsartan lowers blood pressure and may cause symptomatic hypotension. Patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), are at greater risk. If hypotension occurs, consider dose adjustment of diuretics, concomitant antihypertensive drugs, and treatment of other causes of hypotension (e.g., hypovolemia). If hypotension persists despite such measures, reduce the dosage or temporarily discontinue sacubitril/valsartan.	a
Impaired Renal Function; as a consequence of inhibiting the renin-angiotensin-aldosterone system, decreases in renal function may be anticipated in susceptible individuals treated with sacubitril/valsartan. Closely monitor serum creatinine, and down-titrate or interrupt treatment in patients who develop a clinically significant decrease in renal function.	a
Hyperkalemia; hyperkalemia may occur with sacubitril/valsartan. Monitor serum potassium periodically and treat appropriately, especially in patients with risk factors for hyperkalemia such as severe renal impairment, diabetes, hypoaldosteronism, or a high potassium diet. Dosage reduction or interruption of treatment may be required.	a

Black Box Warning for Entresto¹

WARNING
<ul style="list-style-type: none"> • <u>When pregnancy is detected, discontinue Entresto® (sacubitril/valsartan) as soon as possible.</u> • <u>Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.</u>

Drug Interactions

Table 7. Drug Interactions^{1,6}

Generic Name	Interacting Medication or Disease	Potential Result
Sacubitril/valsartan	RAAS	Concomitant use of sacubitril/valsartan with an ACEI is contraindicated because of the increased risk of angioedema and with an ARB, because this agent contains valsartan. The concomitant use with aliskiren is contraindicated in patients with diabetes and should be avoided in patients with patients with renal impairment (eGFR <60 mL/min/1.73 m ²).
Sacubitril/valsartan	Potassium-Sparing Diuretics	Concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium.
Sacubitril/valsartan	Lithium	Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with ARBs. Monitor serum lithium levels during concomitant use.
Sacubitril/valsartan	NSAIDs	In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, concomitant use of NSAIDs with sacubitril/valsartan may result in worsening of renal function, including possible acute renal failure. Monitor renal function periodically.

ACEI=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker, eGFR=estimate glomerular filtration rate, NSAID=nonsteroidal anti-inflammatory drugs, RAAS=Renin-Angiotensin-Aldosterone System

Dosage and Administration

Sacubitril/valsartan is contraindicated with concomitant use of an ACEI. If switching from an ACEI to this agent allow a washout period of 36 hours between administrations of the two drugs.

Table 8. Dosing and Administration¹

Generic Name	Adult Dose	Pediatric Dose	Availability
Sacubitril/valsartan	<p><u>Patients with chronic heart failure (NYHA Class II to IV) and reduced ejection fraction:</u> Tablet: initial, 49/51 mg BID; maintenance and maximum, 97/103 mg BID</p> <p><u>Dosage for patients NOT previously taking an ACEI or ARB or previously taking low doses of these agents:</u> Tablet: initial, 24/26 mg BID; maintenance and maximum, 97/103 mg BID</p>	Safety and efficacy in children have not been established.	Tablet: 24/26 mg 49/51 mg 97/103 mg

ACEI=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker, NYHA=New York Heart Association
Drug regimen abbreviations: BID=twice daily

Clinical Guidelines

The 2013 guidelines from the American College of Cardiology Foundation/American Heart Association continue to recommend that all individuals with hypertension and lipid disorders should be controlled according to contemporary guidelines to lower the risk of HF. In addition, other conditions that may lead to or contribute to HF, such as obesity, diabetes mellitus, tobacco use, etc. should be controlled or avoided. Specifically in Stage B-D HF with reduced ejection fraction, individuals should be given an angiotensin converting enzyme inhibitor (ACEI) to prevent symptomatic HF and reduce mortality. If individuals have a contraindication or are intolerant to ACEIs then the use of an ARB is an appropriate alternative. In patients with a recent or remote history of myocardial infarction (MI) or acute coronary syndrome (ACS) and reduced EF, a β-blocker such as bisoprolol, carvedilol or sustained-release metoprolol succinate, is recommended for all patients. In the case of volume overload, in NYHA class II to IV patients, it is recommended to add a diuretic, unless contraindicated, to improve symptoms. The loop diuretics are currently the preferred diuretics. Other alternatives such as the combination of hydralazine and isosorbide dinitrate can be considered for those who cannot be given an ACEI or ARB because of drug intolerance, hypotension or renal insufficiency, unless contraindicated. Aldosterone receptor antagonists are also recommended to reduce morbidity and mortality following an acute MI in patients with a left ventricular ejection fraction (LVEF) ≤ 40% who develop symptoms of HF or who have a history of diabetes mellitus, unless contraindicated.⁴

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
American College of Cardiology Foundation/American Heart Association: Guideline for the Management of Heart Failure (2013) ⁴	<p><u>Pharmacologic treatment for Stage A HF_rEF:</u></p> <ul style="list-style-type: none"> • Hypertension and lipid disorders should be controlled in accordance with contemporary guidelines to lower the risk of HF. • Other conditions that may lead to or contribute to HF, such as obesity, diabetes mellitus, tobacco use and known cardiotoxic agents, should be controlled or avoided. <p><u>Pharmacologic treatment for Stage B HF_rEF (NYHA Class I):</u></p> <ul style="list-style-type: none"> • All patients with a recent or remote history of MI or ACS and reduced EF, ACEI should be used to prevent symptomatic HF and reduce mortality. In patients intolerant of ACEI, ARBs are appropriate unless contraindicated. • In all patients with a recent or remote history of MI or ACS and reduced EF, evidence-based β-blockers should be used to reduce mortality. • In all patients with a recent or remote history of MI or ACS, statins should be used to prevent symptomatic HF and cardiovascular events. • In patients with structural cardiac abnormalities, including LV hypertrophy, in the absence of a history of MI or ACS, blood pressure should be controlled in accordance with clinical practice guidelines for hypertension to prevent symptomatic HF. • ACEIs should be used in all patients with a reduced EF to prevent symptomatic HF, even if they do not have a history of MI. • β-blockers should be used in all patients with a reduce EF to prevent symptomatic HF, even if they do not have a history of MI. <p><u>Pharmacologic treatment for Stage C HF_rEF (NYHA Class I-IV):</u></p> <ul style="list-style-type: none"> • It is recommended to provide treatment with an ACEI or ARB and a β-blocker, unless contraindicated, to reduce morbidity and mortality. • ACEI have shown benefits in patients with mild, moderate or severe symptoms of HF and in patients with or without CAD. • There are no differences between available ACEI in their effects on symptoms or survival. • Treatment with an ACEI should be initiated at low doses followed by

Clinical Guideline	Recommendations
	<p>gradual dose increments if lower doses have been well tolerated. Clinicians should attempt to use doses that have been shown to reduce the risk of cardiovascular events in clinical trials. If these target doses of an ACE inhibitor cannot be used or are poorly tolerated, intermediate doses should be used.</p> <ul style="list-style-type: none"> • ARBs are recommended for individuals who are ACEI intolerant or can be considered as reasonable alternatives to ACEI for first-line therapy for patients with HFrEF. • ARBs may also be considered in persistently symptomatic patients with HFrEF who are already being treated with an ACEI and a β-blocker in whom an aldosterone antagonist is not indicated or tolerated. • Use of bisoprolol, carvedilol or sustained-release metoprolol succinate is recommended for all patients with current or prior symptoms of HFrEF, unless contraindicated. • For all volume overload, in NYHA class II-IV patients: it is recommended to add a diuretic, unless contraindicated, to improve symptoms. The loop diuretics are currently the preferred diuretics. • The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality in persistently symptomatic African Americans with NYHA class III-IV HFrEF receiving optimal therapy with ACEI and β-blockers, unless contraindicated. • The combination of hydralazine and isosorbide dinitrate can be useful in patients with current or prior symptomatic HFrEF who cannot be given an ACEI or ARB because of drug intolerance, hypotension or renal insufficiency, unless contraindicated. • In patients with NYHA class II-IV and who have LVEF \leq 35% with an estimated creatinine clearance $>$ 30 mL/min and potassium level $<$ 5.0 mEq/dL: it is recommended to add an aldosterone antagonist. • Aldosterone receptor antagonists are also recommended to reduce morbidity and mortality following an acute MI in patients with a LVEF \leq 40% who develop symptoms of HF or who have a history of diabetes mellitus, unless contraindicated. • Digoxin can be beneficial in patients with HFrEF, unless contraindicated, to decrease hospitalizations for HF. • Digoxin can also be considered as an addition to the initial regimen in patients with severe symptoms who have not yet responded symptomatically to initial regimen. • Patients with chronic HF with permanent/persistent/paroxysmal AF and an additional risk factor for cardioembolic stroke (history of hypertension, diabetes mellitus, previous stroke or transient ischemic attack or \geq 75 years of age) should receive chronic anticoagulant therapy. • The selection of an anticoagulant agent for permanent/persistent/paroxysmal AF should be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including time in the international normalized ratio therapeutic range if the patient has been taking warfarin. • Chronic anticoagulation is reasonable for patients with chronic HF who have permanent/persistent/paroxysmal AF but are without additional risk factors for cardioembolic stroke. • Omega-3 polyunsaturated fatty acid (PUFA) supplementation is reasonable to use as adjunctive therapy in patients with NYHA class II-IV symptoms and HFrEF or HFpEF, unless contraindicated, to reduce

Clinical Guideline	Recommendations
	<p>mortality and cardiovascular hospitalizations.</p> <ul style="list-style-type: none"> • Drugs known to adversely affect the clinical status of patients with current or prior symptoms of HFrEF are potentially harmful and should be avoided or withdrawn whenever possible (e.g., most antiarrhythmic drugs, most calcium channel-blocking drugs [except amlodipine], NSAIDs, or thiazolidinediones). <p><u>Pharmacologic treatment for Stage C HFpEF:</u></p> <ul style="list-style-type: none"> • Systolic and diastolic blood pressure should be controlled in patients in accordance with published clinical practice guidelines to prevent morbidity. • Coronary revascularization is reasonable in patients with CAD in whom symptoms (angina) or demonstrable MI is judged to be having an adverse effect on symptomatic HFpEF despite GDMT. • Management of AF according to published clinical practice guidelines in patients with HFpEF is reasonable to improve symptomatic HF. • The use of β-blockers, ACEI and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HFpEF. • The use of ARBs might be considered to decrease hospitalizations for patients with HFpEF.

ACEI=angiotensin-converting enzyme inhibitor, ACS=acute coronary syndrome, AF=atrial fibrillation, ARB=angiotensin-receptor blocker, CAD=coronary artery disease, EF=ejection fraction, GDMT=guideline-directed medical therapy, HF=heart failure, HFrEF=heart failure with reduced ejection fraction, HFpEF=heart failure with preserved ejection fraction, LV=left ventricular, LVEF=left ventricular ejection fraction, MI= myocardial infarction, NSAIDs=non-steroidal antiinflammatory drugs, NYHA=New York Heart Association

Conclusions

Entresto® (sacubitril/valsartan) is a combination of sacubitril, a neprilysin inhibitor, and valsartan, an ARB, indicated to reduce the risk of cardiovascular death and hospitalization for HF in patients with chronic HF (NYHA Class II to IV) and reduced EF.¹ It is the only agent currently available that targets both the natriuretic peptide and the RAAS systems. This agent was shown to significantly reduce the rate of cardiovascular death and HF hospitalizations compared to enalapril in the PARADIGM-HF trial. In addition, it was shown to reduce the rate of all-cause mortality compared to enalapril.

It is estimated that the prevalence of HF in the general population is 1.9% and that this clinical condition currently affects more than five million adults in the U.S. The prevalence of HF is projected to increase by 25% by 2030.⁷ The relative incidence of HFrEF (LVEF \leq 40%) in HF patients is approximated to be 50%.⁴ The remainder of the individuals who fall into the HFpEF category remain a concern as an accurate diagnosis is challenging and efficacious therapies have not been identified.⁴

Sacubitril/valsartan joins another recent HF agent approval, Corlanor® (ivabradine), for the management of chronic HFrEF. In contrast to Corlanor® (ivabradine) which was being recommended as add-on therapy to current standard of care, this new agent was being evaluated as a substitution for current ACEI/ARB therapy which is considered one of the cornerstones of HF therapy. Current treatment guidelines in the U.S. have not yet been updated to include recommendations for the use of either one of these agents. The guidelines do, however, recommend a combination of standard pharmacologic therapies for these individuals (unless contraindicated) to reduce the risk of hospitalization and death. This includes the use of an ACEI or ARB together with a β -blocker for all patients with stable heart failure with reduced LVEF (unless contraindicated) to reduce the risk of hospitalization and death. In addition, diuretics, aldosterone antagonists, hydralazine and isosorbide dinitrate can be added depending on the symptoms and heart failure severity.^{4,8}

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**DIVISION OF HEALTH CARE FINANCING AND POLICY
NEVADA MEDICAID
DRUG USE REVIEW (DUR) BOARD
PROPOSED PRIOR AUTHORIZATION CRITERIA**

Therapeutic Class: Entresto (sacubitril/valsartan)

Last Reviewed by the DUR Board:

Entresto (sacubitril/valsartan) is subject to prior authorization.

1. Coverage and limitations:

Authorization will be given if the following criteria are met and documented:

- a. Diagnosis of chronic heart failure NYHA class II to IV
AND
- b. Left ventricular ejection fraction (LVEF) \leq 35%
AND
- c. Member is \geq 18 years of age
AND
- d. Prescriber is a cardiologist or there is documentation in the recipient's medical record that a cardiologist has been consulted
AND
- e. The recipient has been stabilized on angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) for at least four weeks prior to initiation of therapy
AND
- f. The recipient will not concurrently receive an ACE inhibitor
AND
- g. The recipient is on a maximally tolerated dose of a beta-blocker or the recipient has a contraindication to beta-blocker use
AND
- h. Entresto will be given twice daily with a maximum dose of 97/103 mg twice daily.

2. Prior Authorization Guidelines:

- a. Prior Authorization approval length will be one year.

3. Quantity Limitations:

- a. Entresto (sacubitril/valsartan): 60 tablets/30 days