# Entresto (Sacubitril/Valsartan): First-in-Class Angiotensin Receptor Neprilysin Inhibitor FDA Approved for Patients with Heart Failure

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Heart failure affects an estimated 5.7 million patients aged ≥20 years in the United States, according to the 2009-2012 National Health and Nutrition Examination Survey.[1] Approximately 870,000 new cases of heart failure occur annually. Heart failure is projected to affect more than 8 million individuals aged ≥18 years in the United States by 2030, representing a 46% increase from 2012.[1] The incidence of heart failure is substantially higher in the elderly population, approaching 10 of 1000 people aged ≥65 years.[1]

Heart failure is a life-threatening condition that occurs when the heart cannot pump enough blood and oxygen to meet the body's needs.[2] Approximately 50% of patients with heart failure die within 5 years of diagnosis.[3] In fact, heart failure was a contributing cause of death in 1 of 9 deaths in 2009.[3] The common causes of heart failure include coronary artery disease, diabetes, obesity, and hypertension.[2] The lifetime risk for heart failure in people with blood pressure >90 mm Hg is twice that of those with blood pressure <140 mm Hg/90 mm Hg.[1]

The symptoms of heart failure include dyspnea, fatigue and weakness, edema, persistent cough, rapid or irregular heartbeat, and anginal pain.[2,4] Heart failure is generally categorized into 4 classes (class I-IV) based on symptom severity, as delineated in the New York Heart Association (NYHA) functional classification system (**Table 1**).

Ejection fraction is a key measurement in assessing the heart's ability to pump out blood and in diagnosing and monitoring heart failure.[5] A substantial number of patients with heart failure have a normal ejection fraction. A preserved ejection fraction (ie, diastolic heart failure) indicates that the heart muscle contracts normally, but the ventricles do not relax as they should; a reduced ejection fraction (ie, systolic heart failure) indicates that the heart muscle does not contract effectively and less oxygen-rich blood is pumped out to the body.[5]

In addition to its high mortality rate and considerable impact on an individual's overall health and daily life, heart failure is associated with serious complications, including kidney damage or failure, heart valve problems, heart rhythm problems, and liver damage.[2]

Overall, the societal and economic burden of heart failure is staggering.[6] In the United States, heart failure accounted for $31 billion in total annual costs in 2012.[7] Of this total, approximately $21 billion was attributed to direct medical costs and nearly $10 billion to indirect costs (eg, lost productivity from morbidity and premature mortality); hospitalizations accounted for an estimated 80% of the direct costs attributed to heart failure.[7] In fact, heart failure is the leading cause of hospitalizations in patients aged ≥65 years.[8,9] Furthermore, the total direct medical cost of heart failure is projected to increase from $21 billion in 2012 to $70 billion by 2030.[7] Heart failure also expends more Medicare dollars than any other diagnosis.[6]

The early diagnosis and treatment of heart failure are essential to improving patients' quality and duration of life.[3] Nonpharmacologic approaches to treating heart failure include behavioral and dietary changes, physical activity, and daily symptom tracking.[3] Heart failure prevention involves managing conditions that lead to this condition, including coronary artery disease, hypertension, diabetes, and obesity. In some cases, surgery is used to treat an underlying cause of heart failure.[2]

Pharmacologic treatments for heart failure typically comprise a combination of drugs depending on the symptoms.[2] Until recently, these drugs included renin-angiotensin system inhibitors, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers, in addition to beta-blockers, diuretics, aldosterone antagonists, inotropes, and digoxin.[2]

## FDA Approves Sacubitril plus Valsartan for Chronic Heart Failure

On July 7, 2015, the US Food and Drug Administration (FDA) approved sacubitril plus valsartan (Entresto; Novartis) to reduce the risk for cardiovascular (CV) death and hospitalization in patients with chronic heart failure (NYHA Class II-IV) associated with reduced ejection fraction.[10,11] Sacubitril plus valsartan oral com-

bination is the first angiotensin receptor neprilysin inhibitor to receive FDA approval for this indication.[12]

Valsartan (Diovan) was initially approved by the FDA in 1996 for the treatment of hypertension[13] and in 2002 for the treatment of heart failure.[13,14] In 2005, valsartan received FDA approval to reduce CV mortality in clinically stable patients with left ventricular (LV) failure or with LV dysfunction after a myocardial infarction.[13,15]

The FDA granted the new oral combination a fast-track review, based on its potential to treat a serious or life-threatening condition and fill an unmet need.[10]

"Heart failure is a leading cause of death and disability in adults,"[10] said Norman Stockbridge, MD, PhD, Director of the Division of Cardiovascular and Renal Products at the FDA Center for Drug Evaluation and Research. "Treatment can help people with heart failure live long and enjoy more active lives."[10]

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Milton Packer, MD, lead investigator and Professor and Chair, Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas, commented, "The very meaningful survival advantage of Entresto seen in the PARADIGM-HF trial should persuade physicians to consider Entresto for all appropriate patients, in place of traditional ACE inhibitors or angiotensin receptor blockers."[16] Dr Packer added, "Entresto is expected to change the management of patients with HFrEF [heart failure with reduced ejection fraction] for years to come."[16]

## Mechanism of Action

Sacubitril is a neprilysin inhibitor and valsartan is an angiotensin receptor blocker.[11] The combination of sacubitril plus valsartan inhibits neprilysin (neutral endopeptidase) via LBQ657, the active metabolite of the prodrug sacubitril, and blocks the angiotensin II type-1 ($AT_1$) receptor via valsartan.[11] Valsartan inhibits the effects of LBQ657, and the simultaneous inhibition of the effects of angiotensin II by valsartan. Valsartan inhibits the effects of angiotensin II by selectively blocking the $AT_1$ receptor; it also inhibits angiotensin II–dependent aldosterone release.[11]

Via multimodal action, sacubitril plus valsartan enhances the beneficial response of the neurohormonal system of the heart while inhibiting the damaging effects of the renin-angiotensin-aldosterone system.[17]

## Dosing and Administration

The recommended starting dose of sacubitril plus valsartan is 49 mg of sacubitril/51 mg of valsartan twice daily.[11] The dose is doubled after 2 to 4 weeks to the target maintenance dose of 97 mg of sacubitril/103 mg of valsartan twice daily, as tolerated by the patient.[11]

A reduced starting dose of 24 mg of sacubitril/26 mg of valsartan twice daily should be used in patients who are not currently taking an ACE inhibitor or an angiotensin II receptor blocker, or previously taking a low dose of these agents; patients with severe renal impairment; and patients with moderate hepatic impairment.[11] The dose is doubled every 2 to 4 weeks to the target maintenance dose of 97 mg/103 mg (sacubitril/valsartan) twice daily, as tolerated by the patient.[11]

Sacubitril plus valsartan is available as film-coated tablets in several strengths, including 24 mg/26 mg; 49 mg/51 mg; and 97 mg/103 mg.[11]

## Clinical Trials

The FDA approval of sacubitril plus valsartan was based on results from the PARADIGM-HF clinical trial involving 8442 patients with symptomatic chronic heart failure (NYHA Class II-IV) and systolic dysfunction.[11,18]

**Table 1 NYHA Functional Classification of Heart Disease Severity**

| Class | Functional capacity/symptoms |
|---|---|
| I | Physical activity is not limited<br>Typical physical activity does not result in undue fatigue, palpitation, dyspnea, or anginal pain |
| II | Some limitation of physical activity<br>The patient is comfortable at rest<br>Typical physical activity causes fatigue, palpitation, dyspnea, or anginal pain |
| III | Considerable physical limitation<br>The patient is comfortable at rest<br>Less than ordinary physicial activity results in fatigue, palpitation, dyspnea, or anginal pain |
| IV | Inability to conduct any physical activity without discomfort<br>The patient has symptoms of heart failure even at rest<br>Increased discomfort with any physical activity |

NYHA indicates New York Heart Association.
Adapted from the American Heart Association. Classification of functional capacity and objective assessment. 1994. http://my.americanheart.org/professional/StatementsGuidelines/ByPublicationDate/PreviousYears/Classification-of-Functional-Capacity-and-Objective-Assessment_UCM_423811_Article.jsp. Accessed July 27, 2015.

**Table 2** PARADIGM-HF Study: Effect of Sacubitril plus Valsartan versus Enalapril on the Primary Composite End Point, Its Components, and All-Cause Mortality

| Outcome | Sacubitril plus valsartan, N (%) (N = 4187) | Enalapril, N (%) (N = 4213) | Hazard ratio | *P* value |
|---|---|---|---|---|
| **Primary composite end point** | 914 (21.8) | 1117 (26.5) | 0.80 (95% CI, 0.73-0.87) | <.001 |
| CV death as first event | 377 (9.0) | 459 (10.9) | | |
| Heart failure hospitalization as first event | 537 (12.8) | 658 (15.6) | | |
| **Patients with events**[a] | | | | |
| CV death[b] | 558 (13.3) | 693 (16.5) | 0.80 (95% CI, 0.71-0.89) | |
| Heart failure hospitalizations | 537 (12.8) | 658 (15.6) | 0.79 (95% CI, 0.71-0.89) | |
| **All-cause mortality** | 711 (17.0) | 835 (19.8) | 0.84 (95% CI, 0.76-0.93) | .009 |

[a]Analyses of the components of the primary composite end point were not prospectively planned to be adjusted for multiplicity.
[b]Includes patients who had heart failure hospitalization before death.
CV indicates cardiovascular; CI, confidence interval.
*Sources*: Entresto (sacubitril and valsartan) tablets prescribing information; July 2015; McMurray JJV, et al; for the PARADIGM-HF Investigators and Committees. *N Engl J Med.* 2014;371:993-1004.

**Table 3** Adverse Reactions Reported in ≥5% of Patients Receiving Sacubitril plus Valsartan versus Enalapril in the PARADIGM-HF Study

| Adverse event | Sacubitril plus valsartan, % (N = 4203) | Enalapril, % (N = 4229) |
|---|---|---|
| Hypotension | 18 | 12 |
| Hyperkalemia | 12 | 14 |
| Cough | 9 | 13 |
| Dizziness | 6 | 5 |
| Renal failure or acute renal failure | 5 | 5 |

*Source*: Entresto (sacubitril and valsartan) tablets prescribing information; July 2015.

This study was stopped early after a median follow-up of 27 months, when sacubitril plus valsartan crossed the prespecified margin for a significant reduction in the risks for CV death and hospitalizations in patients with heart failure compared with enalapril.[11,18]

### *PARADIGM-HF: Sacubitril plus Valsartan versus Enalapril Alone*

The primary objective of the PARADIGM-HF trial was to determine whether treatment with sacubitril plus valsartan was superior to enalapril, a renin-angiotensin system inhibitor, in reducing the risk for the combined end point of CV death or hospitalization for heart failure.[11,18] The primary end point was the first event in the composite of CV death or hospitalization for heart failure. The median follow-up duration was 27 months, and patients received treatment for up to 4.3 years.[11,18]

The patients' mean age was 64 years.[11] At the time of randomization, 70% of patients had NYHA Class II, 24% had NYHA Class III, and 0.7% had NYHA Class IV heart failure. The mean LV ejection fraction was 29%.[11] The underlying cause of heart failure was coronary artery disease in 60% of patients; 71% had a history of hypertension, 43% had a history of myocardial infarction, 37% had an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 $m^2$, and 35% had diabetes mellitus.[11]

Based on a time-to-event analysis, sacubitril plus valsartan was superior to enalapril in reducing the risk for the combined end point of CV death or hospitalization in patients with heart failure; the treatment effect reflected a reduction in CV death and heart failure hospitalization (**Table 2**).[11,18] Overall, sacubitril plus valsartan reduced the risk for death from CV causes by 20%, reduced the risk for hospitalization for heart failure by 21%, and reduced heart failure–related symptoms and physical limitations compared with enalapril.[16,18]

Sudden death accounted for 45% of CV deaths, followed by pump failure, which accounted for 26% of CV deaths.[11] In addition, sacubitril plus valsartan improved overall survival—a finding driven entirely by a lower incidence of CV mortality with sacubitril plus valsartan treatment (Table 2).[11]

The PARADIGM-HF study researchers concluded that, "This robust finding provides strong evidence that combined inhibition of the angiotensin receptor and neprilysin is superior to inhibition of the renin-angiotensin system alone in patients with chronic heart failure."[18]

## Adverse Events

The most common adverse reactions (incidence ≥5%) with sacubitril plus valsartan included hypotension, hyperkalemia, cough, dizziness, and renal failure (**Table 3**).[11] In the double-blind period of the PARADIGM-HF study, safety was evaluated in 4203 patients who received sacubitril plus valsartan versus 4229 patients who received enalapril. Patients used sacubitril plus valsartan for up to 4.3 years, with a median exposure of 24 months; 3271 patients received treatment for more than 1 year.[11] Overall, 10.7% of patients who received sacubitril plus valsartan discontinued treatment because of an adverse event versus 12.2% of patients who received enalapril.[11]

## Contraindications

The use of sacubitril plus valsartan is contraindicated in patients with hypersensitivity to any component of sacubitril plus valsartan; in patients with a history of angioedema related to previous use with an ACE inhibitor or an angiotensin II receptor blocker therapy; with concomitant use of ACE inhibitors; and with concomitant use of aliskiren in patients with diabetes.

## Drug Interactions

***Dual blockade of the renin-angiotensin-aldosterone system.*** The concomitant use of sacubitril plus valsartan with an ACE inhibitor is contraindicated, because of the increased risk for angioedema.[11] Because sacubitril plus valsartan contains the angiotensin II receptor blocker valsartan, it should not be used with another angiotensin II receptor blocker. The concomitant use of sacubitril plus valsartan with aliskiren (Tekturna) is contraindicated in patients with diabetes. In addition, the use of aliskiren should be avoided in patients with renal impairment.[11]

***Potassium-sparing diuretics.*** The concomitant use of potassium-sparing diuretics, potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium levels.[11]

***Nonsteroidal anti-inflammatory drugs (NSAIDs).*** The concomitant use of NSAIDs, including COX-2 inhibitors, with sacubitril plus valsartan may lead to the worsening of renal function in patients who are elderly, volume-depleted, or those with compromised renal function. Renal function should be monitored periodically.[11]

***Lithium.*** There is an increased risk for lithium toxicity during the concomitant administration of lithium with angiotensin II receptor antagonists.[11]

## Warnings and Precautions

***Boxed warning.*** Sacubitril plus valsartan should be discontinued as soon as possible when pregnancy is detected.[11] In addition, drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.[11]

***Fetal toxicity.*** Sacubitril plus valsartan can cause fetal harm when administered to a pregnant woman.[11] When pregnancy is detected, the use of this drug should be discontinued and alternative treatment should be considered.[11]

***Angioedema.*** Sacubitril plus valsartan may cause angioedema.[11] If angioedema occurs, therapy should be discontinued immediately, appropriate therapy should be provided, and the patient should be monitored for airway compromise; sacubitril plus valsartan must not be readministered.[11] Sacubitril plus valsartan should not be used in patients with a known history of angioedema related to previous use of an ACE inhibitor or an angiotensin II receptor blocker therapy.[11]

***Hypotension.*** Sacubitril plus valsartan lowers blood pressure and may cause symptomatic hypotension.[11] Patients with an activated renin-angiotensin system, including patients with volume and/or salt depletion (eg, patients receiving high doses of diuretics), are at a greater risk for developing hypotension. If hypotension occurs, dose adjustment of diuretics, concomitant antihypertensive drugs, and treatment of other causes of hypotension should be considered. If hypotension persists, the sacubitril plus valsartan dose should be reduced, or treatment should be temporarily discontinued.[11]

***Impaired renal function.*** Decreases in renal function may be anticipated in susceptible individuals who receive sacubitril plus valsartan.[11] Sacubitril plus valsartan should be down-titrated or interrupted in patients who develop a clinically significant decrease in renal function.[11]

***Hyperkalemia.*** Hyperkalemia may occur with sacubitril plus valsartan therapy.[11] Serum potassium levels should be monitored periodically; patients with risk factors for hyperkalemia, including severe renal impairment, diabetes, hypoaldosteronism, or a high potassium diet should receive appropriate treatment. Dosage reduction or interruption of sacubitril plus valsartan may be required.[11]

## Use in Specific Populations

***Pregnancy.*** Sacubitril plus valsartan can cause fetal harm.[11] An alternative drug treatment should be considered and sacubitril plus valsartan should be discontinued when pregnancy is detected.[11]

***Lactation.*** Breast-feeding is not recommended during treatment with sacubitril plus valsartan, because of the potential for serious adverse reactions from the exposure to this medication.[11]

***Pediatric use.*** The safety and efficacy of sacubitril plus valsartan have not been established in pediatric patients.[11]

***Geriatric use.*** No relevant pharmacokinetic differences were observed in elderly (>65 years) or in very elderly (≥75

years) patients compared with the overall population.[11]

***Renal impairment.*** A starting dose of 24 mg of sacubitril/26 mg of valsartan twice daily is recommended for patients with severe renal impairment (eGFR <30 mL/min/1.73 $m^2$).[11] The dose should be doubled every 2 to 4 weeks to the target maintenance dose of 97 mg of sacubitril/103 mg of valsartan twice daily, as tolerated by the patient. No dose adjustment is required when in patients with mild or moderate renal impairment.[11]

***Hepatic impairment.*** A starting dose of 24 mg of sacubitril/26 mg of valsartan twice daily is recommended for patients with moderate hepatic impairment (Child-Pugh B classification).[11] The dose should be doubled every 2 to 4 weeks to the target maintenance dose of 97 mg of sacubitril/103 mg of valsartan twice daily, as tolerated by the patient. No dose adjustment is required in patients with mild hepatic impairment.[11] The use of sacubitril plus valsartan is not recommended in patients with severe hepatic impairment.[11]

## Conclusion

The FDA approval of sacubitril plus valsartan made available a novel, oral treatment option for patients with heart failure. The first-in-class angiotensin receptor neprilysin inhibitor sacubitril plus valsartan demonstrated a significant mortality benefit in patients with heart failure with reduced ejection fraction in the PARADIGM-HF trial, a head-to-head study that compared sacubitril plus valsartan with enalapril.

Sacubitril plus valsartan may have an important therapeutic role in reducing the risk for CV death and hospitalizations in patients with heart failure associated with reduced ejection fraction. ■

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