

Sacubitril and Valsartan (ENTRESTO™) National Drug Monograph September 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information¹

Description/Mechanism of Action

ENTRESTO (sacubitril and valsartan) is a combination containing a neprilysin inhibitor (sacubitril) and an angiotensin II receptor blocker or ARB (valsartan). Neprilysin is a neutral endopeptidase that degrades endogenous vasoactive peptides including natriuretic peptides, bradykinin, adrenomedullin, and angiotensin II. Inhibition of neprilysin increases the levels of several of these substances, reducing vasoconstriction and sodium retention. The ARB component inhibits angiotensin II by selectively blocking the angiotensin II type-I (AT₁) receptor, reducing vasoconstriction and aldosterone release.

Indication(s) Under Review in this document

Sacubitril/valsartan is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure (HF) in patients with chronic New York Heart Association (NYHA) Class II to IV HF and reduced ejection fraction. The product information states that sacubitril/valsartan is usually used in patients receiving other therapies for HF, in place of an angiotensin-converting enzyme inhibitor (ACEI) or other ARB.

Dosage Form(s) Under Review

Sacubitril/valsartan is available as unscored, ovaloid, biconvex, film-coated tablets in the following strengths: 24/26 mg; 49/51 mg; 97/103 mg.

REMS

REMS No REMS Post-marketing surveillance

See Other Considerations for additional REMS information

Pregnancy

Sacubitril/valsartan contains a Boxed Warning for fetal toxicity; with discontinuation of the product recommended as soon as possible once pregnancy is detected.

Executive Summary

Efficacy^{1,2}

- Results from the Prospective Comparison of ARNI [Angiotensin Receptor-Neprilysin Inhibitor] with ACEI [Angiotensin-Converting-Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF) reported that patients with NYHA Class II-IV heart failure and reduced ejection fraction treated with sacubitril/valsartan (referred to as LCZ696 in the trial) experienced a significant reduction in the primary endpoint of cardiovascular death or first heart failure hospitalizations compared to enalapril (21.8% vs. 26.5%, respectively; HR 0.80, 95% CI 0.73 to 0.87; P<0.001). There was also a reduction in cardiovascular death (HR 0.80, 95% CI 0.71 to 0.89; P<0.001), first HF hospitalizations (HR 0.79, 95% CI 0.71 to 0.89; P<0.001), and all-cause mortality (HR 0.84, 95% CI 0.76 to 0.93; P<0.001) with sacubitril/valsartan compared to enalapril.
- PARADIGM-HF was stopped early due to treatment benefit with sacubitril/valsartan over enalapril after a median follow-up of 27 months.

Safety^{1,2}

- Sacubitril/valsartan is contraindicated in the following: previous hypersensitivity to the drug; history of angioedema with an ACEI or ARB; concomitant treatment with aliskiren in patients with diabetes. Concomitant use of sacubitril/valsartan with an ACEI is also contraindicated; it is recommended that sacubitril/valsartan not be initiated within 36 hours when switching from or to an ACEI.

	<ul style="list-style-type: none"> • Boxed Warning to discontinue sacubitril/valsartan as soon as pregnancy is detected, due to the risk for fetal injury and death. • Additional Warnings and Precautions: <ul style="list-style-type: none"> ○ Angioedema was reported in 0.5% of patients treated with sacubitril/valsartan compared to 0.2% of patients in the enalapril treatment group. If angioedema occurs, sacubitril/valsartan should be discontinued and not re-administered, and the patient provided appropriate therapy and monitoring for airway compromise. ○ Hypotension was reported as an adverse event in 18% of patients treated with sacubitril/valsartan compared to 12% of patients receiving treatment with enalapril. Patients who are volume and/or salt-depleted are at increased risk for developing hypotension with sacubitril/valsartan. ○ Impaired kidney function may result in certain patients treated with sacubitril/valsartan as a result of its inhibition of the renin-angiotensin-aldosterone system (RAAS). Renal failure was reported as an adverse event in 5% of patients in both the sacubitril/valsartan and enalapril treatment groups in one clinical trial. ○ Hyperkalemia was reported as an adverse event in 12% of patients treated with sacubitril/valsartan vs. 14% of patients receiving treatment with enalapril.
Other Considerations ¹⁻⁵	<ul style="list-style-type: none"> • Patients enrolled in PARADIGM-HF were previously receiving treatment with an ACEI or ARB, and for 4 weeks prior to screening were on a stable dose of a beta-blocker and a dose of an ACEI or ARB equivalent to at least enalapril 10 mg daily. The product information includes a statement that sacubitril/valsartan is usually used in addition to other treatments for HF, in place of an ACEI or other ARB, but also provides recommendations for initiation of therapy with sacubitril/valsartan in patients not previously treated with an ACEI or ARB. • The run-in period of PARADIGM-HF consisted of treatment with enalapril 10 mg twice daily for 2 weeks; if no intolerable side effects, this was followed by treatment with sacubitril/valsartan for 4 to 6 weeks (reported in the trial as starting at 100 mg twice daily, then increased to 200 mg twice daily). To minimize the risk for angioedema with overlapping treatment, enalapril was withheld for a day prior to receiving sacubitril/valsartan, which was then withheld for a day prior to randomization. The product information recommends a wash-out period of 36 hours to minimize the risk for angioedema from overlapping therapy. • The target dose of enalapril in PARADIGM-HF was 10 mg twice daily. The mean daily dose of enalapril in the PARADIGM-HF clinical trial was 18.9±3.4 mg. How sacubitril/valsartan compares to a higher target dose of enalapril (i.e., 20 mg twice daily) is unknown at this time. • Approximately 93% of patients enrolled in PARADIGM-HF were receiving concomitant therapy with a beta-blocker; over 50% of patients were also receiving a mineralocorticoid antagonist. • Only ~ 7% of patients who participated in PARADIGM-HF were from North America, with black patients comprising only 5.1% of the overall patient population. The VA provides care for a higher percentage of black patients (~12%) than were included in PARADIGM-HF. As with the ACEIs, the product information for sacubitril/valsartan states that it is associated with a higher rate of angioedema in black patients (2.4%; vs. 0.5% with enalapril) compared to non-black patients (0.4%).
Projected Place in Therapy ¹⁻⁵	<ul style="list-style-type: none"> • Patients with chronic NYHA Class II-IV heart failure and reduced ejection fraction ($\leq 35\%$) currently being treated with a beta-blocker (at a stable dose; after titration to maximally tolerated target doses as recommended by clinical practice guidelines) and an ACEI at a dose equivalent to enalapril 10 mg twice daily (or ARB equivalent to valsartan 160 mg twice daily) may benefit from treatment with sacubitril/valsartan to reduce cardiovascular mortality and heart failure hospitalizations. Preferential treatment with a mineralocorticoid receptor antagonist should also be considered given the long-term outcome benefit in

patients with HF and with the majority of patients in PARADIGM-HF were being treated with this class of medications. It is unknown if there would be any additional benefit in switching patients currently receiving higher target doses of an ACEI (e.g., equivalent to enalapril 20 mg twice daily) to sacubitril/valsartan; the risk vs. benefit of switching to sacubitril/valsartan or continuing present management at a higher target dose ACEI should be taken into consideration. The increased risk for angioedema with sacubitril/valsartan in black patients should also be taken into consideration. The combination of hydralazine and isosorbide dinitrate was found to reduce mortality and hospitalization and is recommended in African American patients who remain symptomatic despite treatment with an ACEI, beta-blocker and mineralocorticoid receptor antagonist and may also be a treatment option. All patients initiated on sacubitril/valsartan should be educated on the potential risk for angioedema and when to seek medical attention if severe angioedema with the potential for airway compromise were to occur.

Background

Purpose for review

Recent FDA approval.

Issues to be determined:

- ✓ Does the evidence show that sacubitril/valsartan reduces long-term outcomes in patients with heart failure with reduced ejection fraction compared to standard therapy?
- ✓ Does sacubitril/valsartan offer advantages over current VA National Formulary (VANF) agents?
- ✓ Determine the most appropriate patients for treatment with sacubitril/valsartan?
- ✓ Are there safety concerns in the Veteran population that may not have been addressed in the clinical trials (e.g., potential increased risk for angioedema with sacubitril/valsartan in black patients)?
- ✓ What additional safety issues need to be considered with the use of sacubitril/valsartan?
- ✓ Does sacubitril/valsartan have specific characteristics best managed by the non-formulary process or criteria for use?

Other therapeutic options^{1,3}

Sacubitril/valsartan includes a neprilysin inhibitor (sacubitril) which is a new drug entity, and an ARB (valsartan). Sacubitril/valsartan was directly compared to treatment with an ACEI, which is recommended as standard therapy in patients with HF. Currently available ACEIs on the VANF are noted below. Although PARADIGM-HF did not compare sacubitril/valsartan to treatment with an ARB, the product labeling mentions treatment in place of an ACEI or ARB; therefore, the ARBs available on the VANF are also noted.

ACEI	VANF	Restriction	ARB	VANF	Restriction
Benazepril	Yes	None	Azilsartan	No	NA
Captopril	Yes	None	Candesartan	No	NA
Enalapril	Yes	None	Eprosartan	No	NA
Fosinopril	Yes	None	Irbesartan	No	NA
Lisinopril	Yes	None	Losartan	Yes	None
Perindopril	No	NA	Olmesartan	No	NA
Quinapril	No	NA	Telmisartan	No	NA
Ramipril	Yes	None	Valsartan	Yes	HF
Trandolapril	No	NA			

Efficacy (FDA Approved Indications)^{1,2,6}

Literature Search Summary

A literature search was performed on PubMed/Medline (1990 to July 2015) using the search terms LCZ696, sacubitril and valsartan, angiotensin neprilysin inhibition. The search was limited to clinical trials performed in humans and published in the English language. Randomized controlled Phase 3 trials published in peer-reviewed journals evaluating the FDA approved indications were included. Reference lists were searched for relevant articles providing additional information.

Review of Efficacy^{1,2}

- FDA approval of sacubitril/valsartan was based on the pivotal Prospective Comparison of ARNI [Angiotensin Receptor-Neprilysin Inhibitor] with ACEI [Angiotensin-Converting-Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial.
- Results from PARADIGM-HF demonstrated a statistically significant reduction in the composite primary outcome (death from cardiovascular causes or first hospitalization for heart failure) with sacubitril/valsartan (also referred to as LCZ696) compared to enalapril (21.8% vs. 26.5%, respectively; HR 0.80, 95% CI 0.73 to 0.87; P<0.001). There was also a reduction in the individual components of the primary endpoint as well as all-cause mortality with sacubitril/valsartan compared to treatment with enalapril. Patients enrolled in the trial had NYHA Class II-IV HF with a reduced ejection fraction and elevated B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-pro-BNP), were on treatment with a stable dose of a beta-blocker, and had been receiving treatment with an ACEI or ARB.
- Overall, there is moderate quality of evidence for the use of sacubitril/valsartan in patients with heart failure to reduce cardiovascular mortality and HF hospitalizations compared to treatment with enalapril (Refer to Appendix A).

PARADIGM-HF^{2,6}

- PARADIGM-HF was a Phase 3 multicenter, multinational, double-blind, parallel group, active-controlled trial in patients with NYHA Class II-IV symptoms and ejection fraction $\leq 40\%$ (changed to $\leq 35\%$ after protocol amendment), and a BNP ≥ 150 pg/ml (or NT-pro-BNP ≥ 600 pg/ml) or a BNP ≥ 100 pg/ml (or NT-pro-BNP ≥ 400 pg/ml) if the patient had been hospitalized for heart failure in the past 12 months. Prior to screening, patients taking an ACEI or ARB (any dose) were required to take a stable dose of a beta-blocker and an ACEI or ARB considered equivalent to at least 10 mg enalapril daily.
- Exclusion criteria: symptomatic hypotension; systolic blood pressure (SBP) < 100 mm Hg at screening or 95 mm Hg at randomization; estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m² body-surface area at screening or a decrease in eGFR $> 25\%$ (amended to 35%) during the period between screening and randomization; serum potassium > 5.2 mmol/L at screening or > 5.4 mmol/L at randomization; hepatic disease (e.g., aspartate aminotransferase or alanine aminotransferase > 2 times the upper limit of normal, history of hepatic encephalopathy, esophageal varices, or porto-caval shunt); history of angioedema; or unacceptable side effects during treatment with an ACEI or ARB.
- Enalapril run-in phase: 10,513 patients were switched from their previous treatment of an ACEI or ARB to single-blind enalapril 10 mg twice daily for two weeks (median 15 days). Approximately 10.5% of patients discontinued at this point (5.6% due to an adverse event; 0.6% due to abnormal laboratory or other test result).
- Sacubitril/valsartan run-in phase: 9419 patients who tolerated the enalapril run-in phase and were eligible to continue were then switched from enalapril to sacubitril/valsartan (LCZ696 100 mg) twice daily, with an increase to 200 mg twice daily, for 4 to 6 weeks (median 29 days). Approximately 10.4% of patients discontinued at this point (5.8% due to an adverse event; 0.6% due to abnormal laboratory or other test result). Enalapril was withheld for a day prior to receiving sacubitril/valsartan, and sacubitril/valsartan was withheld for a day prior to randomization into the study, to minimize the risk for angioedema from overlapping therapy.
- Ultimately, 4187 patients were randomized to sacubitril/valsartan (LCZ696 200 mg) twice daily and 4212 patients to enalapril 10 mg twice daily (43 patients were excluded after randomization due to invalid randomization procedures or because they were from sites closed due to violations).

- Select baseline characteristics are included in the table below.

PARADIGM-HF Select Baseline Characteristics²

Characteristic	Sacubitril/Valsartan (N=4187)	Enalapril (N=4212)
Age	64	64
Male	79.0%	77.4%
Race/ethnicity		
White	66.0%	66.0%
Black	5.1%	5.1%
Asian	18.1%	17.8%
Region of trial participants		
North America	7.4%	6.9%
Latin America	17.0%	17.1%
Western Europe and other	24.5%	24.3%
Central Europe	33.3%	34.0%
Asia-Pacific	17.8%	17.6%
Left ventricular ejection fraction	29.6%	29.4%
New York Heart Association Functional Class		
II	71.6%	69.3%
III	23.1%	24.9%
Previous treatment		
Angiotensin-converting enzyme inhibitor	78.0%	77.5%
Angiotensin II receptor blocker	22.2%	22.9%
Treatment at randomization		
Beta-blocker	93.1%	92.9%
Mineralocorticoid antagonist	54.2%	57.0%

- The PARADIGM-HF trial was stopped early due to treatment benefit (based on cardiovascular mortality) with sacubitril/valsartan compared to enalapril after a median follow-up of 27 months.
- Patients treated with sacubitril/valsartan experienced a significant reduction in the primary endpoint of combined cardiovascular death or HF hospitalizations compared to enalapril. There was also a reduction in cardiovascular death, first hospitalization due to worsening HF, and all-cause mortality with sacubitril/valsartan compared to enalapril. Additional secondary endpoints included the change in the Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score from baseline to 8 months, time to new onset of atrial fibrillation, and time to first occurrence of a decline in kidney function (defined as end-stage renal disease or decrease in eGFR \geq 50% or decrease of > 30 ml/min/1.73 m² body-surface area from randomization to < 60 ml/min/1.73 m²). Results of the primary and secondary endpoints are included in the table below.

PARADIGM-HF Primary and Secondary Outcome Results²

Outcome	Sacubitril/Valsartan (N=4187)	Enalapril (N=4212)	HR (95% CI)	P
	Number (%)			
Composite primary endpoint	914 (21.8)	1117 (26.5)	0.80 (0.73-0.87) ^a	<0.001
CV mortality	558 (13.3)	693 (16.5)	0.80 (0.71-0.89) ^b	<0.001
First HF hospitalization	537 (12.8)	658 (15.6)	0.79 (0.71-0.89) ^c	<0.001
Secondary outcomes				
All-cause mortality	711 (17.0)	835 (19.8)	0.84 (0.76-0.93)	<0.001
Change in KCCQ score	-2.99 \pm 0.36	-4.63 \pm 0.36	1.64 ^d (0.63-2.65)	0.001
New onset AF	84 (3.1)	83 (3.1)	0.97 (0.72-1.31)	0.83
Kidney function decline	94 (2.2)	108 (2.6)	0.86 (0.65-1.13)	0.28

Composite primary endpoint=CV mortality or first hospitalization for worsening HF
AF=atrial fibrillation; CI=confidence interval; CV=cardiovascular; HF=heart failure; HR=hazard ratio; KCCQ=Kansas City Cardiomyopathy Questionnaire (change in clinical summary score at 8 months; scale of 0 to 100 with higher score indicating fewer symptoms and physical limitations due to heart failure)

^a NNT (number needed to treat to prevent one event)=21 over 27 months

^b NNT=32 over 27 months

^c NNT=36 over 27 months

^d Between group point difference

- Mean daily doses of sacubitril/valsartan (LCZ696 target dose 200 mg twice daily) were 375±71 mg and 18.9±3.4 mg for enalapril (target dose 10 mg twice daily).
- The trial was sponsored by Novartis. The published results state the study data were collected, managed, and analyzed by the sponsor per a predefined plan, with the analysis replicated by an independent academic statistician.

Potential Off-Label Use^{7,8}

- Sacubitril/valsartan (LCZ696) has also been studied for the treatment of hypertension⁷ and for HF with preserved ejection fraction.⁸ Sacubitril/valsartan is not recommended for treatment of these conditions until long-term outcome data on the safety and efficacy in these patient populations can be evaluated.

Safety^{1,2}

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning¹	<ul style="list-style-type: none"> • WARNING: FETAL TOXICITY <ul style="list-style-type: none"> ○ Discontinue sacubitril/valsartan as soon as pregnancy is detected. ○ Drugs that act on the RAAS can cause fetal injury and death. <p><i>[see Warnings and Precautions]</i></p>
Contraindications¹	<ul style="list-style-type: none"> • Hypersensitivity to any component of sacubitril/valsartan • History of angioedema with an ACEI or ARB • Concomitant use with an ACEI; it is recommended that sacubitril/valsartan not be initiated within 36 hours when switching from or to an ACEI • Concomitant treatment with aliskiren in patients with diabetes
Warnings/Precautions¹	<ul style="list-style-type: none"> • Fetal Toxicity: There is the potential for sacubitril/valsartan to cause fetal harm if administered to a pregnant woman. Drugs that act on the RAAS administered during the second and third trimesters of pregnancy reduce fetal renal function and increase fetal and neonatal morbidity and death. Discontinue sacubitril/valsartan as soon as pregnancy is detected and consider alternate treatment. If there are no appropriate alternative medications to those acting on the RAAS, or if the drug is considered lifesaving to the mother, the pregnant patient should be advised of the potential risk to the fetus. • Angioedema: Angioedema was reported in 0.5% of patients treated with sacubitril/valsartan compared to 0.2% of patients in the enalapril treatment group. Patients with a history of angioedema may be at increased risk of angioedema with sacubitril/valsartan; sacubitril/valsartan is contraindicated in patients with a history of angioedema attributed to an ACEI or ARB. It is noted that black patients have a higher rate of angioedema compared to non-black patients. If angioedema occurs, sacubitril/valsartan should be discontinued and not re-administered, and the patient provided appropriate therapy and monitoring for airway compromise. Angioedema with laryngeal involvement may be fatal. • Hypotension: Hypotension was reported as an adverse event in 18% of patients treated with sacubitril/valsartan compared to 12% of patients receiving treatment with enalapril. Patients who are volume and/or salt-depleted are at increased risk for developing hypotension with sacubitril/valsartan. • Impaired Kidney Function: Impaired kidney function may result in certain patients treated with sacubitril/valsartan as a result of its inhibition of the RAAS. Renal failure was reported as an adverse event in 5% of patients in both the sacubitril/valsartan and enalapril treatment groups in PARADIGM-HF. As with other agents that act on the RAAS, kidney function should be closely monitored in patients treated with sacubitril/valsartan, with dose adjustments or discontinuation as indicated. • Hyperkalemia: Hyperkalemia was reported as an adverse event in 12% of patients treated with sacubitril/valsartan vs. 14% of patients receiving

treatment with enalapril. Periodically monitor potassium in patients treated with sacubitril/valsartan, especially in patients with risk factors for hyperkalemia, with dose adjustments or discontinuation as indicated.

Safety Considerations^{1,2}

- In PARADIGM-HF, it was reported that angioedema occurred in 19 patients treated with sacubitril/valsartan (0.5%) compared to 10 patients treated with enalapril (0.2%) (P=0.13), which was confirmed by blinded adjudication. Hospitalization or use of catecholamines or glucocorticoids was required in 9 patients on sacubitril/valsartan and 5 patients on enalapril. No patients required mechanical intervention due to airway compromise.² The incidence of angioedema in black patients was reported to be 2.4% with sacubitril/valsartan compared to 0.5% with enalapril.¹
- Symptomatic hypotension was reported in 588 (14.0%) patients receiving sacubitril/valsartan vs. 388 (9.2%) patients in the enalapril treatment group (P<0.001); symptomatic hypotension with a SBP < 90 mm Hg occurred in 112 (2.7%) patients on sacubitril/valsartan and 59 (1.4%) patients on enalapril (P<0.001).

Adverse Reactions^{1,2}

Common adverse reactions ^{1,2} (PARADIGM-HF)	The most common adverse events reported in the sacubitril/valsartan compared to the enalapril treatment group, respectively, include: hypotension (18% vs. 12%); cardiac failure (17% vs. 20%); hyperkalemia (12% vs. 14%); renal impairment (10% vs. 12%); cough (9% vs. 13%); dizziness (6% vs. 5%).
Death/Serious adverse reactions ²	In PARADIGM-HF, 46% of patients treated with sacubitril/valsartan experienced at least one serious adverse event (SAE) compared to 51% of patients in the enalapril treatment group. Cardiac failure was reported as the most common SAE occurring in 14% of patients in the sacubitril/valsartan treatment group and 15% on enalapril. Other select SAEs were reported as follows for sacubitril/valsartan vs. enalapril, respectively: death 1.33% vs. 1.84%; hypotension 1.40% vs. 1.61%; renal failure 1.02% vs. 1.28%. ² No additional information is provided on the deaths reported as a serious adverse event.
Discontinuations due to adverse reactions ²	Sacubitril/valsartan vs. enalapril, respectively: overall 10.7% vs. 12.3% (P=0.03); hypotension 36 (0.9%) vs. 29 (0.7%) (P=0.38); renal impairment 29 (0.7%) vs. 59 (1.4%) (P=0.002); hyperkalemia 11 (0.3%) vs. 15 (0.4%) (P=0.56)

Drug Interactions¹

Drug-Drug Interactions^{1,3}

- **Dual RAAS blockade:** Concomitant administration of sacubitril/valsartan with an ACEI is contraindicated due to the risk for angioedema. Use of sacubitril/valsartan with an ARB should be avoided since sacubitril/valsartan contains an ARB. Use of sacubitril/valsartan with aliskiren is contraindicated in patients with diabetes; avoid concomitant use with aliskiren in patients with impaired kidney function (eGFR < 60 ml/min/1.73m²).
- **Potassium-sparing diuretics:** Concomitant use of sacubitril/valsartan with potassium-sparing diuretics, potassium supplements, or salt substitutes containing potassium may increase serum potassium levels.
- **Nonsteroidal Anti-Inflammatory Drugs (NSAIDs); Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors):** Concomitant use of sacubitril/valsartan with NSAIDs or COX-2 inhibitors in patients who are elderly, volume-depleted or receiving diuretics, or have impaired kidney function, may result in worsening renal function, with the potential for acute kidney failure. It is recommended to periodically monitor kidney function in these patients. In general, these agents are not recommended in patients with heart failure given their association with increased morbidity and mortality.³
- **Lithium:** As concomitant use of an ARB in patients on treatment with lithium have resulted in increased serum lithium concentrations and lithium toxicity, serum lithium levels should be monitored in patients treated with sacubitril/valsartan and lithium.

Risk Evaluation

As of July 31, 2015

Comments

Sentinel event advisories

- None

Look-alike/sound-alike error potentials

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Sacubitril/valsartan 24/26mg, 49/51mg, 97/103mg	None	None	None	Sildenafil Secukinumab
Entresto	None	None	None	Entereg Entyvio

- Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations^{1-6,9-12}

- Patients enrolled in PARADIGM-HF were previously receiving treatment with an ACEI or ARB, and for 4 weeks prior to screening were on a stable dose of a beta-blocker and a dose of an ACEI or ARB equivalent to at least enalapril 10 mg daily. The product information includes a statement that sacubitril/valsartan is usually used in addition to other treatments for HF, in place of an ACEI or other ARB, but also provides recommendations for initiation of therapy with sacubitril/valsartan in patients not previously treated with an ACEI or ARB. The safety and efficacy of sacubitril/valsartan in patients who did not receive a pretrial of either an ACEI or ARB is unknown at this time.^{1,2}
- The run-in period of PARADIGM-HF consisted of treatment with enalapril 10 mg twice daily for 2 weeks; if no intolerable side effects, this was followed by treatment with sacubitril/valsartan for 4 to 6 weeks (reported in the trial as starting at 100 mg twice daily, then increased to 200 mg twice daily). To minimize the risk for angioedema with overlapping treatment, enalapril was withheld for a day before receiving sacubitril/valsartan, which was then withheld a day before randomization. The product information recommends a wash-out period of 36 hours to minimize the risk for angioedema from overlapping therapy.^{1,2}
- The target dose of enalapril in PARADIGM-HF was 10 mg twice daily. The mean daily dose of enalapril in the PARADIGM-HF clinical trial was 18.9±3.4 mg. How sacubitril/valsartan compares to a higher target dose of enalapril (i.e., 20 mg twice daily) is unknown at this time.^{1-3,6,9}
- The target dose of sacubitril/valsartan in PARADIGM-HF was 200 mg twice daily, with the ARB component equivalent to 160 mg valsartan (with 160 mg twice daily being the recommended target dose of valsartan). The mean daily dose of sacubitril/valsartan was 375±71 mg. The target dose of the approved product of sacubitril/valsartan is 97/103 mg twice daily.¹⁻³
- Approximately 93% of patients enrolled in PARADIGM-HF were receiving concomitant therapy with a beta-blocker; over 50% of patients were also receiving a mineralocorticoid receptor antagonist. Given the significant benefit of treatment with a mineralocorticoid receptor antagonist in reducing cardiovascular mortality and HF hospitalizations (by 37%), and all-cause mortality (by 24 to 30%), in patients with HF and reduced ejection fraction, treatment with this class of medications should be considered prior to sacubitril/valsartan in appropriate patients. Considering treatment with a mineralocorticoid receptor antagonist was also part of the protocol for PARADIGM-HF.^{1-3,6,10,11}
- Only ~ 7% of patients who participated in PARADIGM-HF were from North America, with black patients comprising only 5.1% of the overall patient population. The VA provides care for a higher percentage of black patients (~12%) than were included in PARADIGM-HF. As with the ACEIs, the product information for sacubitril/valsartan states that it is associated with a higher rate of angioedema in black patients (2.4%; vs. 0.5% with enalapril) compared to non-black patients (0.4%).^{1,2,4,5} The manufacturer will be tracking reports of angioedema in black patients as part of a post-marketing request from the FDA.
- Median follow-up in PARADIGM-HF was 27 months; whether long-term neprilysin inhibition will have an adverse effect on other conditions (e.g., Alzheimer's disease) is unknown at this time.^{1,12} There is a post-marketing requirement for the manufacturer to track FDA MedWatch reports with sacubitril/valsartan related to cognition.

Dosing and Administration¹

- **Patients currently on an ACEI:** Concomitant use of sacubitril/valsartan with an ACEI is contraindicated. Patients being switched from an ACEI to sacubitril/valsartan should have their ACEI discontinued for 36 hours prior to initiating sacubitril/valsartan at the recommended dose of 49/51 mg twice daily. The dose should then be doubled at 2 to 4 weeks to the target maintenance dose of 97/103 mg twice daily, as tolerated.
- **Patients not currently treated with an ACEI or ARB, or who were previously receiving low doses of an ACEI or ARB:** The recommended starting dose of sacubitril/valsartan is 24/26 mg twice daily in these patients, doubling the dose every 2 to 4 weeks to the target maintenance dose of 97/103 mg twice daily, as tolerated.
- **Severe renal impairment (eGFR < 30 ml/min/1.73m²):** The recommended starting dose of sacubitril/valsartan is 24/26 mg twice daily, doubling the dose every 2 to 4 weeks to the target maintenance dose of 97/103 mg twice daily, as tolerated.
- **Moderate hepatic impairment (Child-Pugh B):** The recommended starting dose of sacubitril/valsartan is 24/26 mg twice daily, doubling the dose every 2 to 4 weeks to the target maintenance dose of 97/103 mg twice daily, as tolerated. Use in severe hepatic impairment is not recommended.

Special Populations (Adults)¹

	Comments
Elderly	<ul style="list-style-type: none"> • It was reported that there were no relevant pharmacokinetic differences noted in patients ≥ 65 years or ≥ 75 years of age.
Pregnancy	<ul style="list-style-type: none"> • Boxed Warning for fetal toxicity; discontinuation is recommended as soon as possible once pregnancy is detected. Drugs that act on the RAAS administered during the second and third trimesters of pregnancy reduce fetal renal function and increase fetal and neonatal morbidity and death. In animal studies with sacubitril/valsartan, there was an increase in embryo/fetal death and teratogenicity. It is recommended to discontinue sacubitril/valsartan as soon as pregnancy is detected and consider alternate treatment. If there are no appropriate alternative medications to those acting on the RAAS, or if the drug is considered lifesaving to the mother, the pregnant patient should be advised of the potential risk to the fetus.
Lactation	<ul style="list-style-type: none"> • No data are available in humans; however, sacubitril/valsartan has been found to be present in rat milk. Due to the potential for serious adverse reactions in the breastfed infant, it is recommended that either breastfeeding or the drug should be discontinued.
Renal Impairment	<ul style="list-style-type: none"> • No dose adjustments recommended in patients with mild (eGFR 60 to 90 ml/min/1.73m²) to moderate (eGFR 30 to 60 ml/min/1.73m²) renal impairment; the starting dose in patients with severe (eGFR < 30 ml/min/1.73m²) renal impairment is 24/26 mg twice daily.
Hepatic Impairment	<ul style="list-style-type: none"> • No dose adjustments in patients with mild hepatic impairment; in moderate hepatic impairment (Child-Pugh B) the initial dose of 24/26 mg twice daily is recommended; use of sacubitril/valsartan in patients with severe hepatic impairment (Child-Pugh C) is not recommended as it has not been studied in this patient population.
Pharmacogenetics/genomics	<ul style="list-style-type: none"> • No data identified.

Projected Place in Therapy

- Approximately 5.7 million patients in the U.S. have heart failure, with > 850,000 new cases diagnosed each year.¹³ Heart failure increases with age, and it is estimated that over 5% of patients who receive care from the VA have a primary diagnosis of HF.¹⁴ Mortality rates are high, at approximately 50% within 5 years of being diagnosed with HF.^{3,13}
- Several pharmacologic treatments have been shown to reduce mortality and hospitalizations in patients with HF.³ Evidence-based guideline directed medical therapy includes an ACEI (or ARB, if ACEI intolerant) and a beta-blocker (i.e., bisoprolol, carvedilol, or metoprolol succinate) for most patients. Treatment with a mineralocorticoid receptor antagonist has also been shown to reduce morbidity and mortality in patients with

HF, and is recommended where appropriate and in patients where safety can be monitored.³ Digoxin may be considered in patients with persistent symptoms despite guideline directed medical therapy, to reduce HF hospitalizations.³ The combination of hydralazine and isosorbide dinitrate was found to reduce mortality and hospitalization and is recommended in African American patients who remain symptomatic despite treatment with an ACEI, beta-blocker and mineralocorticoid receptor antagonist.³

- Patients with chronic NYHA Class II-IV heart failure and reduced ejection fraction ($\leq 35\%$) currently being treated with a beta-blocker (at a stable dose; after titration to maximally tolerated target doses as recommended by clinical practice guidelines) and an ACEI at a dose equivalent to enalapril 10 mg twice daily (or ARB equivalent to valsartan 160 mg twice daily) may benefit from treatment with sacubitril/valsartan to reduce cardiovascular mortality and heart failure hospitalizations. The safety and efficacy of sacubitril/valsartan in patients who did not receive a pretrial of either an ACEI or ARB is unknown at this time. Preferential treatment with a mineralocorticoid receptor antagonist should also be considered given the long-term outcome benefit in patients with HF and with the majority of patients in PARADIGM-HF were being treated with this class of medications. It is unknown if there would be any additional benefit in switching patients currently receiving higher target doses of an ACEI (e.g., equivalent to enalapril 20 mg twice daily) to sacubitril/valsartan; the risk vs. benefit of switching to sacubitril/valsartan or continuing present management at a higher target dose ACEI should be taken into consideration. The increased risk for angioedema with sacubitril/valsartan in black patients should also be taken into consideration. All patients initiated on sacubitril/valsartan should be educated on the potential risk for angioedema and when to seek medical attention if severe angioedema with the potential for airway compromise were to occur.
- Overall, there is moderate quality of evidence for the use of sacubitril/valsartan in patients with heart failure to reduce cardiovascular mortality and HF hospitalizations compared to treatment with enalapril (Refer to Appendix A as well as sections on Efficacy and Other Considerations).

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Appendix A: GRADEing the Evidence

Designations of Quality

<u>Quality of evidence designation</u>	<u>Description</u>
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High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
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Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
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Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.
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Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. *Ann Intern Med* 2010;153:194-199.