Formulary Drug Reviews

Sacubitril/Valsartan

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Generic Name:	Sacubitril/Valsartan
Proprietary Name:	Entresto (Novartis)
Approval Rating:	1P NME
Therapeutic Class:	Angiotensin II Receptor Antagonists, Neprilysin Inhibitor
Similar Drugs:	Omapatrilat, Valsartan
Sound- and Look-Alike Names:	Olmesartan, Losartan, Valsartan, Irbesartan

INDICATIONS

Sacubitril/valsartan (LCZ696) is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (New York Heart Association [NYHA] class II to IV) and reduced ejection fraction.¹⁻⁴ Sacubitril/valsartan can be used concurrently with other heart failure therapies in place of an angiotensin converting enzyme (ACE) inhibitor or other angiotensin II receptor blocker (ARB).⁴

Sacubitril/valsartan has also been studied for the treatment of essential hypertension in adult patients.⁵⁻⁷ It is currently being compared head to head with olmesartan in patients 60 years and older to determine the effects on aortic stiffness and central aortic hemodynamics in the PARAMETER study. This 52-week trial is assessing the impact of these drugs on central aortic systolic pressure and pulse pressure; results are expected in 2015.⁸ Preliminary work is also being conducted to determine whether sacubitril/valsartan has a potential role in modulating cardiac remodeling after a myocardial infarction (MI).⁹

CLINICAL PHARMACOLOGY

Management of heart failure with reduced ejection fraction (HFrEF) (systolic heart failure) is multimodal with medications from various classes including ACE inhibitors, ARBs, beta-blockers, mineralocorticosteroid antagonists, and diuretics.¹⁰ Activation of the angiotensin II type 1 receptor contributes to elevated blood pressure through vasoconstriction and aldosterone secretion, which leads to sodium and water retention.^{11,12}

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Neprilysin is an enzyme expressed in the kidney that is responsible for the degradation of several endogenous substances, including C-type natriuretic peptide, atrial natriuretic peptide, B-type natriuretic peptide (BNP), endothelin-1, kinin peptides, opioid peptides, substance P, amyloid beta protein, gastrin, and angiotensin I.¹² Natriuretic peptides (types A and B) promote vasodilation and natriuresis, inhibit abnormal growth of the ventricles, suppress the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system, inhibit the release and action of vasopressin, and augment the parasympathetic nervous system.¹³ Accumulation of some of these substances reduces blood pressure and theoretically improves cardiovascular outcomes.¹² Sacubitril (AHU377) is a prodrug of LBQ657, which is a neprilysin inhibitor.¹⁴

Angiotensin II is a pressor agent from the RAAS with effects that include release of aldosterone, cardiac stimulation, and reabsorption of sodium in the kidneys. These 3 mechanisms lead to elevated blood pressure. Valsartan blocks the binding of angiotensin II to the angiotensin II type 1 receptor, leading to a decrease in blood pressure.¹¹

Administration of multiple doses of sacubitril/valsartan (a fused molecule that contains 1:1 molar ratio of valsartan and sacubitril) leads to increases in plasma cyclic guanosine monophosphate, renin concentration and activity, and angiotensin II.^{5,14,15} The clinical relevance of the changes in neurohormone concentrations is not clear, although a relationship between baseline plasma renin and reduction in mean diastolic blood pressure (DBP) was observed.⁵ In a clinical trial of patients with heart failure with preserved ejection fraction (HFpEF) (diastolic heart failure), sacubitril/valsartan treatment caused a reduction in high-sensitivity troponin, which was associated with improved cardiac structure, myocardial injury, n-terminal prohormone brain natriuretic peptide (NT-proBNP), and left atrial size.¹⁶

PHARMACOKINETICS

After oral administration of the sacubitril/valsartan tablet, the compound dissociates into sacubitril and valsartan. The time to maximum plasma concentration following a single dose of sacubitril/valsartan is 1.5 to 2.2 hours for valsartan, 0.5 to 1.1 hours for sacubitril, and 1.9 to 3.5 hours for LBQ657.^{4,14} The oral bioavailability of sacubitril is 60% or greater. Valsartan in this formulation has better bioavailability than valsartan in other marketed tablet formulations; equivalent doses for valsartan 26, 51, and 103 mg in the *Entresto* tablets would be 40, 80, and 160 mg tablets, respectively,

with other marketed tablet formulations.^{4,14} Administration with food had no clinically meaningful effects on the systemic exposures of sacubitril, LBQ657, or valsartan; there is a decreased systemic exposure to valsartan when administered with food but it had no effect on the drug's therapeutic effect.⁴

All 3 compounds (sacubitril, LBQ657, and valsartan) are highly bound (94% to 97%) to plasma protein. The apparent volume of distribution is 103 L for sacubitril and 75 L for valsartan. The ability of LBQ657 to cross the blood-brain barrier is poor (0.28%).⁴

Sacubitril is converted to LBQ657 by esterases. LBQ657 is not metabolized and valsartan undergoes minimal metabolism (20%). Urinary excretion of sacubitril (mainly as LBQ657) is 52% to 68% of the oral dose and is approximately 13% for valsartan and its metabolites. The portion of the dose found in the feces for sacubitril (mainly as LBQ657) is 37% to 48%; for valsartan and its metabolites, it is 86%.⁴ Mean half-life of each compound was 1.1 to 3.6 hours for sacubitril, 9.9 to 11.1 hours for LBQ657, and 8.9 to 16.6 hours for valsartan.^{4,14} Steady-state concentrations are achieved in 3 days with twice-daily oral administration.⁴ Both the maximal drug concentration (C_{max}) and area under the curve (AUC) exhibit an approximately linear relationship with increased dose; peak plasma concentration occurs at 1.6 to 4.9 hours for valsartan, 0.6 to 0.9 hours for sacubitril, and 1.8 to 2.7 hours for LBQ657 with repeated daily dosing.¹⁴ No accumulation was reported after 14 days of dosing for either valsartan or sacubitril, but LBQ657 has minimal accumulation.^{4,14}

Gender had no effect on the pharmacokinetics of sacubitril/valsartan, but pharmacokinetics of LBQ657 and valsartan were different between younger (18 to 45 years of age) and older subjects (older than 65 years). When compared to younger patients, LBQ657 kinetics in the elderly population demonstrated a 42% increase in AUC and a 30% increase in half-life; peak plasma concentrations were unaffected by age. Increases were also observed in the elderly for valsartan kinetic parameters, including AUC (30%), peak plasma concentration (24%), and half-life (3.35 hours). However, none of these differences were considered clinically significant and did not warrant an adjustment in dose.¹⁷

COMPARATIVE EFFICACY

Indication: Treatment of Chronic Heart Failure with Reduced Ejection Fraction

Entresto contains sacubitril (24 mg, 49 mg, or 97 mg) and valsartan (26 mg, 51 mg, or 103 mg).

Dosing in clinical trials was based on the total amount of both components (ie, 24/26 mg, 49/51 mg, and 97/103 mg were referred to as 50 mg, 100 mg, and 200 mg, respectively). The dose in approved product labeling lists the milligram strength of the individual components of the combination tablet: sacubitril 24 mg/valsartan 26 mg, sacubitril 49 mg/valsartan 51 mg, and sacubitril 97 mg/valsartan 103 mg. To reduce the risk of errors, include the doses of both ingredients (eg, *Entresto* 24/26 mg) when prescribing *Entresto*.⁴

Guidelines: 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Task Force guideline for the management of heart failure: A report of the ACCF/AHA Task Force on Practice Guidelines

Reference: Yancy CW, et al, 2013¹⁰

Comments: In patients with stage A heart failure, hypertension and lipid control should be initiated. The guidelines recommend treatment of hypertension with diuretics, ACE inhibitors, ARBs, or beta-blockers, but not calcium channel blockers or alpha-blockers. Stage B patients with a history of MI or acute coronary syndrome and reduced ejection fraction should be initiated on an ACE inhibitor or ARB if intolerant of ACE inhibitors; additional treatment should include a beta-blocker, but nondihydropyridine calcium channel blockers should not be used. Stage C patients with reduced ejection fraction should be treated with an ACE inhibitor or ARB, beta-blocker, or aldosterone receptor antagonist, and diuretics should be used for symptom control in patients with reduced ejection fraction. Digoxin may be beneficial in decreasing hospitalizations, and patients with atrial fibrillation and an additional risk factor for stroke should receive chronic anticoagulant therapy. African American patients with NYHA class III or IV should be treated with hydralazine and isosorbide to reduce morbidity and mortality. At the time of the publication of these guidelines, sacubitril/valsartan was not approved.

Studies

Drug: Sacubitril/Valsartan vs Enalapril

Reference: McMurray JJ, et al, 2014 (PARADIGM-HF study)^{13,18-20}

Study Design: Randomized, double-blind, active-controlled, multicenter study

Study Funding: Novartis

Patients: 8,442 patients 18 years and older with heart failure (NYHA functional class II to IV); left ventricular ejection fraction (LVEF) 35% or lower; plasma BNP 150 pg/mL or higher (or NT-proBNP 600 pg/mL or higher) at screening, or BNP 100 pg/mL or higher (or NT-proBNP 400 pg/mL or higher) and a hospitalization within the previous 12 months for heart failure; previous treatment for at least 4 weeks with a stable dose of an ACE inhibitor or ARB equivalent to enalapril 10 mg/day; and treatment with a stable dose of a beta-blocker for at least 4 weeks (unless contraindicated or not tolerated). Additionally, it was encouraged that an aldosterone antagonist be considered in all patients; if administered, the aldosterone antagonist dose needed to be stable for at least 4 weeks prior to screening. Key exclusion criteria included known hypersensitivity to any of the drugs, contraindications to any of the study drugs, history of intolerance to study drugs, acute decompensated heart failure, symptomatic hypotension, estimated glomerular filtration rate (GFR) less than 30 mL/min at screening or a greater than 35% decline between visits 1 and 3 or between visits 1 and 5, and history of severe pulmonary disease. Patients could have a cardiac resynchronization therapy device as long as it was implanted more than 3 months prior to visit 1. Mean age was 64 years; 22% of patients were female, and 66% were White; 70% of patients were NYHA class II and 24% were NYHA class III; mean LVEF was 29%; 71% of patients had hypertension and 37% had a history of atrial fibrillation; mean creatinine clearance (CrCl) was 68 mL/min. Concurrent treatments included beta-blockers (93%), diuretics (80%), mineralocorticoid receptor antagonists (60%), digoxin (30%), anticoagulants (32%), any antiplatelet (including aspirin and/or adenosine diphosphate antagonist) (57%), lipid-lowering agents (56%), implantable cardioverter defibrillator (15%), cardiac resynchronization therapy (7%), and cardiac resynchronization therapy with defibrillator (5%).

Intervention: The study consisted of 4 phases, including a screening visit, a single-blind run-in period to enalapril 10 mg twice daily, a single-blind run-in period to sacubitril/valsartan 200 mg (as sacubitril 97 mg/valsartan 103 mg) twice daily, and a randomized double-blind treatment period. Patients were then randomized 1:1 to receive sacubitril/valsartan 200 mg (sacubitril 97 mg/valsartan

103 mg) twice daily or enalapril 10 mg twice daily until death from a cardiovascular event or heart failure hospitalization.

Results

Primary Endpoint(s)

- Proportion of patients with the primary composite outcome of death from cardiovascular causes or hospitalization for heart failure at 27 months was 21.8% in the sacubitril/valsartan group and 26.5% in the enalapril group (hazard ratio [HR], 0.8; 95% confidence interval [CI], 0.73 to 0.87; $P < .001$); number needed to treat (NNT) was 21.3 (reported as 21).

Secondary Endpoint(s)

- Proportion of patients who died from cardiovascular causes at 27 months was 13.3% in the sacubitril/valsartan group and 16.5% in the enalapril group (HR, 0.8; 95% CI, 0.71 to 0.89; $P < .001$); NNT was 31.25 (reported as 32).^{18,19} The most frequent cardiovascular causes were sudden cardiac death (HR, 0.8; 95% CI, 0.68 to 0.94; $P = .008$) and death due to worsening heart failure (HR, 0.79; 95% CI, 0.64 to 0.98; $P = .034$), both of which were reduced with sacubitril/valsartan compared with enalapril therapy. Deaths due to MI, stroke, and non-cardiovascular causes were distributed evenly between the 2 treatments.²¹
- Proportion of patients hospitalized for heart failure at 27 months was 12.8% in the sacubitril/valsartan group and 15.6% in the enalapril group (HR, 0.79; 95% CI, 0.71 to 0.89; $P < .001$); NNT was 35.7.
- Proportion of patients who died from any cause at 27 months was 17% in the sacubitril/valsartan group and 19.8% in the enalapril group (HR 0.84; 95% CI, 0.76 to 0.93; $P < .001$); NNT was 35.7.
- Change in Kansas City Cardiomyopathy Questionnaire at 8 months was -2.99 points in the sacubitril/valsartan group and -4.63 in the enalapril group; treatment difference was 1.64 points (95% CI, 0.63 to 2.65; $P = .001$); sensitivity analysis using last observation carried forward supports the significance of this improvement.
- Number of patients with new-onset atrial fibrillation was 84 in the sacubitril/valsartan group and 83 in the enalapril group ($P = .84$).
- Number of patients with a decline in renal function was 94 in the sacubitril/valsartan group and 108 in the enalapril group ($P = .28$), and number

of patients with progression to end-stage renal disease was 8 in the sacubitril/valsartan group and 16 in the enalapril group ($P = .11$).

Endpoint(s)

- Discontinuations not due to death occurred in 17.8% of patients on sacubitril/valsartan and 19.8% of patients on enalapril ($P = .02$).
- A total of 76% and 75% of sacubitril/valsartan and enalapril patients, respectively, maintained the target dose through the end of the study.²⁰
- Incidence of symptomatic hypotension was 14% with sacubitril/valsartan and 9.2% with enalapril ($P < .001$); number needed to harm (NNH) with sacubitril/valsartan was 20.8.
- Incidence of serum creatinine elevated to at least 2.5 mg/dL was 3.3% with sacubitril/valsartan and 4.5% with enalapril ($P = .007$); NNH with enalapril was 83.3.
- Incidence of serum potassium greater than 6 mmol/L was 4.3% with sacubitril/valsartan and 5.6% with enalapril ($P = .007$); NNH with enalapril was 76.9.
- Incidence of cough was 11.3% with sacubitril/valsartan and 14.3% with enalapril ($P < .001$); NNH with enalapril was 33.3.
- Post hoc analysis: Risk of death or hospitalization for any reason was lower with sacubitril/valsartan compared with enalapril (HR, 0.87; 95% CI, 0.82 to 0.93; $P < .0001$).²⁰
- Post hoc analysis: Proportion of patients requiring addition of new drug, intravenous (IV) therapy, or increased daily dose of diuretic for longer than 1 month was 12.4% with sacubitril/valsartan and 14.3% with enalapril (HR, 0.84; 95% CI, 0.74 to 0.94; $P = .003$); NNT with sacubitril/valsartan was 52.7.
- Post hoc analysis: Proportion of patients evaluated in the emergency department for worsening heart failure but discharged without admission was 2.4% with sacubitril/valsartan and 3.6% with enalapril (HR, 0.66; 95% CI, 0.52 to 0.85; $P = .001$); NNT with sacubitril/valsartan was 83.4.

Comments: This was a phase 3 pivotal trial of clinically stable patients with mild to moderate heart failure. If patients were not tolerating either study drug, the dose could be reduced after discontinuation of drugs with no disease-modifying effects (eg, calcium channel blockers, nitrates, alpha-ARBs). Because a greater proportion of the enalapril group was expected to receive a beta-blocker and

mineralcorticoid antagonist, the sample size was based on expected annual composite event rate of 14.5% and cardiovascular death rate of 7%. Pre-defined subgroup analysis showed improvement in the primary endpoint in all regions/races except Black, Asian, or Native American patients and patients in Western Europe or Asia-Pacific regions. Additional subgroups showing no benefit compared with enalapril were patients with NYHA class III or IV, ejection fraction more than 35%, no prior use of an ACE inhibitor, and age 75 years and older. Rates of adverse events are summarized elsewhere. Number of days in the hospital per admission per patient did not significantly differ ($P = .86$), although both the number of patients and the total number of stays in intensive care were significantly lower with sacubitril/valsartan compared with enalapril ($P = .019$ and $P = .005$, respectively). Post hoc analysis of the SOLVD-Treatment and CHARM-Alternative trials showed a greater reduction (43% relative risk; 95% CI, 34% to 50%; $P < .0001$) in the primary outcome with sacubitril/valsartan compared with placebo.²² Issues surrounding the use of a putative placebo comparison exist, including major differences between trials (eg, background medications) and current guideline recommendations supporting an ACE inhibitor or ARB as the standard of care in almost all patients with heart failure. The guidelines recommend an ARB if the patient is unable to tolerate the ACE inhibitor (eg, due to cough), unless there is a contraindication to its use.¹⁰ Enalapril was selected as the active comparator because it was used in the pivotal mortality/morbidity SOLVD-Treatment trial, which established the usefulness of ACE inhibitors in the treatment of patients with HFrEF and because the impact of ARBs on mortality was inconsistent at the time the PARADIGM-HF study was designed.^{13,18} Sacubitril was not combined with enalapril because the concurrent use of a neprilysin inhibitor (eg, sacubitril) with an ACE inhibitor increases the risk of angioedema; however, the combination of valsartan and sacubitril produced a lower risk of angioedema. A potential problem with ACE inhibitors (eg, enalapril) is that they may lose efficacy over time due to redundant angiotensin II-generating pathways, sometimes referred to as “aldosterone escape” pathways, whereas ARBs do not possess

the bradykinin-enhancing properties of ACE inhibitors. As previously mentioned, patients without a history of ACE inhibitor use showed no added benefit for the primary endpoint.

Limitations: Less than 10% of patients included were located in North America.

Drug: Sacubitril/Valsartan vs Valsartan

Reference: Solomon SD, et al, 2012 (PARAMOUNT study)²³

Study Design: Randomized, double-blind, placebo-controlled, multicenter study

Study Funding: Novartis

Patients: 301 patients 40 years and older with NYHA class II or III heart failure and ejection fraction at least 45%, baseline NT-proBNP greater than 400 pg/mL, concomitant diuretic use, systolic blood pressure (SBP) less than 140 mm Hg or less than 160 mm Hg if taking at least 3 antihypertensives, estimated GFR of at least 30 mL/min per modification of diet in renal disease formula, and a serum potassium of 5.2 mmol/L or less. Key exclusion criteria included ejection fraction less than 45% at any time; isolated right heart failure due to pulmonary disease, anemia, severe obesity, primary valvular or myocardial disease; and coronary artery or cerebrovascular disease needing revascularization within 3 months of screening or likely to need revascularization during the trial. Baseline characteristics reported for sacubitril/valsartan and valsartan groups, respectively, were as follows: mean age was 70.9 and 71.2 years; 57% and 56% were female; 81% and 78% were NYHA class II; 56% and 53% used ACE inhibitors at baseline, 38% and 41% used ARBs at baseline, 100% of both groups used diuretics, 79% and 80% used beta-blockers, and 19% and 23% used aldosterone antagonists.

Intervention: Patients were randomized 1:1 to receive sacubitril/valsartan 200 mg (sacubitril 97 mg/valsartan 103 mg) or valsartan 160 mg twice daily for 36 weeks. The start of the study drug was preceded by a 2-week, single-blind, placebo run-in period. Doses were initiated at sacubitril/valsartan 50 mg (sacubitril 24 mg/valsartan 26 mg) and valsartan 40 mg and titrated over 2 to 4 weeks to the final dose. The study duration was 36 weeks; the first 12 weeks was the main study period and the last 24 weeks was classified as an

extension period. Background therapy was at the discretion of the treating physician; however, any previous ACE inhibitor or ARB was discontinued 24 hours before randomization.

Results

Primary Endpoint(s)

- Change in NT-proBNP at 12 weeks was greater with sacubitril/valsartan (−178 pg/mL) compared with valsartan (−27 pg/mL); ratio of change, 0.77 (95% CI, 0.64 to 0.92; $P = .005$).

Secondary Endpoint(s)

- Change in NT-proBNP at 36 weeks was −267 pg/mL with sacubitril/valsartan and −215 pg/mL with valsartan; ratio of change, 0.85 (95% CI, 0.65 to 1.09; $P = .2$).
- Reduction in blood pressure at 12 weeks was 9.3/4.9 mm Hg in the sacubitril/valsartan group and 2.9/2.1 mm Hg in the valsartan group ($P = .001$ for SBP and $P = .09$ for DBP).
- Reduction in blood pressure at 12 weeks was 9.3/4.9 mm Hg in the sacubitril/valsartan group and 2.9/2.1 mm Hg in the valsartan group ($P = .001$ for SBP and $P = .09$ for DBP).
- Both left atrial volume and dimension were reduced at 36 weeks in the sacubitril/valsartan group compared with the valsartan group ($P = .003$ and $P = .034$, respectively).
- No difference was seen in NYHA class improvement at 12 weeks; at 36 weeks, the sacubitril/valsartan group improved compared with the valsartan group ($P = .05$).
- Clinical composite assessment did not differ between either group at 12 or 36 weeks.
- No difference was seen in the Kansas City Cardiomyopathy Questionnaire for either group.
- No difference was seen for echocardiographic measures, including LVEF, ventricular volume, or measures of diastolic function between groups at week 36.

Endpoint(s): Proportion of patients achieving the target dose was 81% in the sacubitril/valsartan group and 78% in the valsartan group. Most commonly reported adverse events were symptomatic hypotension, hyperkalemia, and renal dysfunction.

Comments: This was a phase 2 study. Patients were analyzed as an intent-to-treat (ITT) population at 12 weeks, but week 36 data were analyzed for completers. Completer analysis of the primary endpoint showed similar results to ITT analysis. Missing data were handled with last observation carried forward. Patients were stratified by previous use of

an ACE inhibitor or ARB and by region. Patients with HFpEF showed a reduction in a biomarker that is correlated with improvements in left ventricular wall stress. Monitoring of NT-proBNP is recommended as a prognostic factor.¹⁰ A post hoc analysis found a weak correlation between reductions in SBP and NT-proBNP.²⁴ The study was too short to measure clinical outcomes.

Limitations: The study was not powered or designed to show clinical outcomes. The majority of patients enrolled had NYHA class II heart failure.

Indication: Other Cardiovascular Disease

Studies

Drug: Sacubitril/Valsartan vs Valsartan, Sacubitril, and Placebo

Reference: Ruilope LM, et al, 2010⁵

Study Design: Randomized, double-blind, active-comparator, placebo-controlled, multicenter study

Study Funding: Novartis

Patients: 1,328 patients between 18 and 75 years of age with uncomplicated mild to moderate essential hypertension, defined as a mean sitting DBP of 90 to 109 mm Hg after washout of previous antihypertensives, or 95 to 109 mm Hg for previously untreated patients. Key exclusion criteria included severe hypertension, history of hypersensitivity to ARBs or neprilysin inhibitors, diabetes, secondary hypertension, history or presence of functional cardiac disorder, hepatic or renal disease, clinically important anemia, or abnormal sodium or potassium concentrations. Medications not allowed included antiarrhythmics, nonstudy antihypertensives, tricyclic antidepressants, monoamine oxidase inhibitors, systemic corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), sympathomimetics (long-term use), alpha-adrenergic blockers, cholestyramine, colestipol, and phosphodiesterase inhibitors (within 48 hours of visits). Average age was 53 years; 57% of patients were male, and 87% were White; DBP was 99.7 mm Hg (range, 99 to 100.4 mm Hg) and SBP was 155.7 mm Hg (range, 154.8 to 156.4 mm Hg).

Intervention: Patients were randomized to 1 of 8 groups treated with sacubitril/valsartan 100 mg (sacubitril 49 mg/valsartan 51 mg), sacubitril/valsartan 200 mg (sacubitril 97 mg/valsartan 103 mg), sacubitril/valsartan 400 mg (2 doses of

sacubitril 97 mg/valsartan 103 mg), valsartan 80 mg, valsartan 160 mg, valsartan 320 mg, AHU377 (sacubitril) 200 mg, or placebo once daily. Patients treated with sacubitril/valsartan 400 mg started with sacubitril/valsartan 200 mg for 7 days before increasing the dose; those treated with valsartan 320 mg started with valsartan 160 mg for 7 days before increasing the dose.

Results

Primary Endpoint(s)

- Placebo-subtracted least squares mean (LSM) reduction between the mean change in blood pressure with 3 sacubitril/valsartan doses compared with equivalent valsartan doses at the end of the 8-week treatment period was -2.17 mm Hg (95% CI, -3.28 to -1.06 ; $P < .0001$) for DBP and -4.2 mm Hg (95% CI, -5.94 to -2.46 ; $P < .0001$) for SBP (pooled average difference between sacubitril/valsartan and equivalent valsartan dose when both were compared with baseline).

Secondary Endpoint(s)

- Change in mean SBP for sacubitril/valsartan 100 mg (sacubitril 49 mg/valsartan 51 mg) and valsartan 80 mg was -6.02 mm Hg and -4.72 mm Hg, respectively; treatment difference was not calculated ($P = .4$). Change in DBP for sacubitril/valsartan 100 mg (sacubitril 49 mg/valsartan 51 mg) and valsartan 80 mg was -3.19 and -2.36 mm Hg, respectively; treatment difference was not calculated ($P = .4$).
- Change in mean SBP for sacubitril/valsartan 200 mg (sacubitril 97 mg/valsartan 103 mg) and valsartan 160 mg was -11 mm Hg and -5.69 mm Hg, respectively; treatment difference was -5.28 mm Hg (95% CI, -8.28 to -2.28 ; $P = .0023$). Change in mean DBP for sacubitril/valsartan 200 mg (sacubitril 97 mg/valsartan 103 mg) and valsartan 160 mg was -6.14 mm Hg and -3.17 mm Hg, respectively; treatment difference was -2.97 mm Hg (95% CI, -4.88 to -1.07 ; $P = .0006$).
- Change in mean SBP for sacubitril/valsartan 400 mg (2 doses of sacubitril 97 mg/valsartan 103 mg) and valsartan 320 mg was -12.5 mm Hg and -6.44 mm Hg, respectively; treatment difference was -6.01 mm Hg (95% CI, -9.01 to -3.02 ; $P < .0001$). Change in mean DBP for sacubitril/valsartan 400 mg (2 doses of sacubitril 97 mg/valsartan 103 mg) and valsartan 320 mg was -6.85 mm Hg and -4.15 mm Hg, respectively; treatment difference

was -2.7 mm Hg (95% CI, -4.61 to -0.8 ; $P = .0006$).

- Proportion of patients responding to treatment (DBP less than 90 mm Hg, or at least 10 mm Hg decrease from baseline) was 70% with sacubitril/valsartan 200 mg (sacubitril 97 mg/valsartan 103 mg) compared with 56% with valsartan 160 mg ($P = .0095$), and 74% with sacubitril/valsartan 400 mg (2 doses of sacubitril 97 mg/valsartan 103 mg) compared with 63% with valsartan 320 mg ($P = .0261$).
- Reduction in DBP with AHU377 (sacubitril) 200 mg compared with placebo was -2.99 mm Hg (95% CI, -4.89 to -1.09 ; $P = .0021$); reduction in SBP was -4.2 mm Hg (95% CI, -7.18 to -1.23 ; $P = .0057$).
- There was no difference between any dose of sacubitril/valsartan and corresponding dose of valsartan for 24-hour ambulatory DBP, despite significant reductions in nighttime DBP.
- Both sacubitril/valsartan 200 and 400 mg (sacubitril 97 mg/valsartan 103 mg and 2 doses of sacubitril 97 mg/valsartan 103 mg) produced significantly reduced 24-hour ambulatory SBP compared with corresponding valsartan doses; these results were driven by significant reductions in nighttime SBP, without a significant change in daytime SBP.
- Decreases in pulse pressure were significant for both sacubitril/valsartan 200 and 400 mg (sacubitril 97 mg/valsartan 103 mg and 2 doses of sacubitril 97 mg/valsartan 103 mg) compared with corresponding valsartan doses; reductions were dose related in sacubitril/valsartan groups but not in valsartan groups.
- Increases in SBP and DBP after the withdrawal week were similar for both sacubitril/valsartan and valsartan groups, without a clinically relevant rebound effect.

Endpoint(s): The most commonly occurring adverse event was headache.

Comments: This was a phase 2 proof-of-concept and dose-ranging study. Sacubitril/valsartan 200 mg (sacubitril 97 mg/valsartan 103 mg) and valsartan 160 mg provide similar systematic valsartan exposure. All measurements are trough measurements taken before the daily dose. This study showed increased blood pressure reductions for both the sacubitril/valsartan 200 and 400 mg (sacubitril 97 mg/valsartan 103 mg and 2 doses of sacubitril 97 mg/valsartan 103 mg) doses compared with

corresponding valsartan doses. All reductions in blood pressure are placebo subtracted. This was a surrogate marker study rather than an outcome study. Safety data did not show evidence of angioedema, although a relatively small number of Black patients were enrolled. Kidney function was better preserved, as indicated by statistical differences in estimated GFR and cystatin C; an increase in urinary albumin to creatinine ratio was seen with sacubitril/valsartan compared with valsartan.²⁵

Limitations: The study did not include a large number of Black patients (6% to 11% in each group).

Drug: Sacubitril/Valsartan vs Placebo

Reference: Kario K, et al, 2014⁶

Study Design: Randomized, double-blind, placebo-controlled, multicenter study

Study Funding: Novartis

Patients: 389 Asian patients 18 years and older with mild to moderate uncomplicated essential hypertension. Untreated patients were included if DBP was between 95 and 109 mm Hg and SBP was between 140 and 179 mm Hg at randomization; previously treated patients were included if DBP was between 90 and 109 mm Hg after wash-out, and then if DBP was between 95 and 109 mm Hg and if SBP was between 140 and 179 mm Hg at randomization. Exclusion criteria included severe hypertension (DBP at least 110 mm Hg or SBP at least 180 mm Hg); history of angioedema, diabetes, or secondary hypertension; history or presence of functional cardiac disorder, hepatic or renal disease, clinically important anemia, or abnormal sodium or potassium concentrations. Mean age was 51.6 years, mean DBP was 99.9 mm Hg, mean SBP was 155 mm Hg, and duration of hypertension ranged from 5 to 6.7 years.

Intervention: After a 2-week washout period and a 2-week placebo run-in period, patients were randomized 1:1:1:1 to receive sacubitril/valsartan 100 mg, sacubitril/valsartan 200 mg, sacubitril/valsartan 400 mg (sacubitril 49 mg/valsartan 51 mg, sacubitril 97 mg/valsartan 103 mg, and 2 doses of sacubitril 97 mg/valsartan 103 mg, respectively), or placebo once daily for 8 weeks. Patients treated with sacubitril/valsartan 400 mg (2 doses of sacubitril 97 mg/valsartan 103 mg) were initiated at sacubitril/valsartan 200 mg (sacubitril 97 mg/valsartan 103 mg) for 7 days.

Results

Primary Endpoint(s)

- LSM difference in DBP at 8 weeks was -7.84 , -7.29 , and -8.76 mm Hg for sacubitril/valsartan 100, 200, and 400 mg, respectively ($P < .0001$ for each dose compared with placebo).
- LSM difference in SBP at 8 weeks was -11.86 , -12.57 , and -15.38 mm Hg for sacubitril/valsartan 100, 200, and 400 mg, respectively ($P < .0001$ for each dose compared with placebo).

Secondary Endpoint(s)

- LSM difference in pulse pressure at 8 weeks was -4.01 , -5.4 , and -6.73 mm Hg for sacubitril/valsartan 100, 200, and 400 mg, respectively ($P < .001$ for each dose compared with placebo).
- Proportion of patients achieving blood pressure control was 47%, 49%, 54.2%, and 15.2% for sacubitril/valsartan 100, 200, and 400 mg, and placebo, respectively ($P < .0001$ for each dose compared with placebo).
- LSM difference in 24-hour blood pressure control at 8 weeks was improved for each dose of sacubitril/valsartan compared with placebo ($P < .0001$); these results were similar for daytime and nighttime blood pressure control.
- Increase in DBP after 1 week of single-blind placebo was 8, 8.8, and 11.6 mm Hg for sacubitril/valsartan 100, 200, and 400 mg, respectively.

Endpoint(s): The most commonly reported adverse events were nasopharyngitis and upper respiratory tract infection.

Comments: This phase 2 trial evaluating reduction of blood pressure with sacubitril/valsartan in an Asian population confirmed results of another study with a predominantly White population.² Reductions were compared with placebo only, rather than with an equivalent dose of valsartan. Many therapeutic options are available for the treatment of hypertension, and interruption of the RAAS is not as effective for Asian patients. A head-to-head comparison with an agent of another class would confirm the efficacy of sacubitril/valsartan for the treatment of hypertension. Safety results do not show any new concerns, although the duration of the trial was relatively short.

Limitations: The trial lacked an active comparator.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

Sacubitril/valsartan is contraindicated in patients with hypersensitivity to any component of the

formulation (sacubitril, valsartan, microcrystalline cellulose, low-substituted hydroxypropyl cellulose, crospovidone, magnesium stearate [vegetable origin], talc, colloidal silicon dioxide, hypromellose, titanium dioxide [E 171], Macrogol 4000, talc, and iron oxide red [E 172]). It is also contraindicated in patients with a history of angioedema related to previous ACE inhibitor or ARB therapy, with concomitant use with ACE inhibitors (minimum washout period of 36 hours), and with concomitant use of aliskiren in patients with diabetes.⁴

Warnings and Precautions

Sacubitril/valsartan carries a boxed warning regarding the risk of fetal toxicity.

Sacubitril/valsartan therapy should be discontinued when pregnancy is detected.⁴ Use of drugs acting on the RAAS during the second and third trimesters of pregnancy may lead to increased fetal and neonatal death.^{4,11} Sacubitril/valsartan should also be avoided during lactation; if used, breast-feeding should be discontinued.⁴

There is a risk of angioedema with sacubitril/valsartan. Prior to initiation of sacubitril/valsartan, patients should discontinue therapy with the ACE inhibitor at least 36 hours prior to initiating sacubitril/valsartan. The risk of angioedema is also higher in Black than in non-Black patients. Patients with a history of angioedema, especially to previous ACE inhibitor or ARB therapy, may be at increased risk.^{4,13}

Hypotension leading to dizziness or falls may occur in patients taking sacubitril/valsartan. In patients with volume or salt depletion, correct these depletions prior to initiation with sacubitril/valsartan or start sacubitril/valsartan therapy at a lower dose. If the patient is receiving diuretics, concomitant antihypertensive drugs, or treatment of other causes of hypotension, the dose of these medications should be evaluated and adjusted, if necessary. If hypotension persists after these changes, the dose of sacubitril/valsartan may need to be adjusted again or temporarily discontinued.^{4,11}

Some patients may be at increased risk of decreased renal function. These patients may have preexisting renal artery stenosis, chronic kidney disease, or severe congestive heart failure. Careful monitoring of patients with these conditions is necessary to reduce the incidence of acute renal failure, and dosage adjustments or interruption of therapy may be necessary.^{4,11}

Patients with impaired renal function, diabetes, hypoaldosteronism, or a high-potassium diet who are taking valsartan-containing products may be at increased risk of hyperkalemia. If a patient experiences

hyperkalemia, a reduction in dosage or interruption of sacubitril/valsartan may be required.^{4,11}

Use in patients with severe hepatic impairment is not recommended.⁴

Safety and effectiveness in pediatric patients have not been established.⁴

ADVERSE REACTIONS

The mostly commonly reported adverse reactions (occurring in 5% or more of patients) were hypotension, hyperkalemia, cough, dizziness, and renal failure.⁴ The most commonly reported adverse reactions in published clinical trials of patients treated for heart failure with sacubitril/valsartan or enalapril, respectively, were hypotension (17.6% vs 12%), cardiac failure (17.4% vs 19.7%), hyperkalemia (11.6% vs 14%), renal impairment (10.1% vs 11.5%), cough (8.8% vs 12.6%), and dizziness (6.3% vs 4.9%).¹⁸ Other adverse events included atrial fibrillation, pneumonia, peripheral edema, dyspnea, nasopharyngitis, upper respiratory tract infection, urinary tract infection, diarrhea, bronchitis, angina pectoris, anemia, back pain, influenza, hypokalemia, chronic cardiac failure, congestive heart failure, arthralgia, hypertension, fatigue, diabetes mellitus, gout, renal failure, hyperuricemia, ventricular tachycardia, non-cardiac chest pain, headache, acute renal failure, syncope, chronic obstructive pulmonary disease, insomnia, pain in extremity, asthenia, nausea, death from a cardiovascular event, constipation, pyrexia, acute cardiac failure, and vomiting.^{4,18}

DRUG INTERACTIONS

Use with an ACE inhibitor or other ARB will cause a dual blockade of the renin-angiotensin system and should be avoided. Aliskiren should be avoided in patients with diabetes or patients with renal impairment (estimated GFR less than 60 mL/min/1.73 m²).⁴

Sacubitril/valsartan plus a potassium-sparing diuretic may increase serum potassium levels. Patients requiring dual therapy with these drugs should have their serum potassium level monitored regularly throughout therapy.⁴

Concurrent use with NSAIDs may increase the risk of developing renal impairment.⁴

The addition of sacubitril/valsartan to lithium may result in increased lithium levels and lithium-related toxicities.⁴

Sacubitril/valsartan is a weak inhibitor of cytochrome P450 (CYP-450) 2C9. Warfarin, a drug commonly used in patients with heart failure, is a substrate of CYP2C9. A drug-drug interaction study showed no

significant increase in the exposure of warfarin 25 mg or significant increases in partial thromboplastin time and international normalized ratio. Additionally, no effects on the pharmacokinetics of sacubitril/valsartan 200 mg (sacubitril 97 mg/valsartan 103 mg) twice daily were reported. No adjustment is required when coadministering sacubitril/valsartan and warfarin.²⁶

Coadministration of sacubitril/valsartan 400 mg (2 doses of sacubitril 97 mg/valsartan 103 mg) once daily and carvedilol 25 mg twice daily decreased the peak plasma concentrations of valsartan by 12% but did not affect the pharmacokinetics of sacubitril or carvedilol. No adjustment should be required when coadministering sacubitril/valsartan and carvedilol.²⁷

Coadministration of sacubitril/valsartan 400 mg (2 doses of sacubitril 97 mg/valsartan 103 mg) once daily and metformin 1,000 mg once daily in Japanese patients decreases both the peak plasma concentrations and total exposure of metformin by 23% but does not affect the pharmacokinetics of sacubitril/valsartan. None of these changes were considered clinically relevant.^{28,29}

Coadministration of sacubitril/valsartan 200 mg (sacubitril 97 mg/valsartan 103 mg) twice daily with digoxin 0.25 mg once daily did not affect the pharmacokinetics of sacubitril/valsartan or digoxin. No dose adjustment of either drug should be required when coadministering sacubitril/valsartan and digoxin.³⁰

Coadministration of sacubitril/valsartan 400 mg (2 doses of sacubitril 97 mg/valsartan 103 mg) as a single dose or once daily with omeprazole 40 mg once daily in healthy Japanese subjects did not alter the AUC of sacubitril and the pharmacokinetics of LBQ657, but did decrease the peak plasma concentrations of sacubitril by 7% and the AUC and peak plasma concentrations of valsartan by 11% and 13%, respectively. None of these changes were considered clinically relevant.²⁹

Coadministration of sacubitril/valsartan 400 mg (2 doses of sacubitril 97 mg/valsartan 103 mg) as a single dose or once daily with levonorgestrel 150 mcg/ethinyl estradiol 30 mcg in healthy Japanese subjects had no effect on the pharmacokinetics of ethinyl estradiol and LBQ657, no effect on the AUC of levonorgestrel, decreased the C_{max} of levonorgestrel by 15%, and decreased the AUC and C_{max} of valsartan by 14% and 16%, respectively. None of these changes were considered clinically relevant.²⁹

RECOMMENDED MONITORING

Routine monitoring of blood pressure, NYHA class function, kidney function, and serum electrolytes

should be performed.¹⁸ Additional monitoring for worsening symptoms (eg, jugular venous pressure, peripheral edema, orthopnea) is recommended by guidelines; baseline measurement of BNP or NT-proBNP may help determine prognosis.¹⁰ Reductions in NT-proBNP were seen in 1 trial, but the clinical significance of serial NT-proBNP has not been determined.^{10,23}

DOSING

The recommended starting dose for the treatment of heart failure is sacubitril 49 mg/valsartan 51 mg twice daily with or without food. The dose should be doubled after 2 to 4 weeks to sacubitril 97 mg/valsartan 103 mg twice daily (target maintenance dose), as tolerated by the patient.⁴ The starting dose should be reduced to sacubitril 24 mg/valsartan 26 mg twice daily for patients not currently taking an ACE inhibitor or ARB or who were previously taking a low dose of these agents, for patients with severe renal impairment (estimated GFR less than 30 mL/min/1.73 m²), and for patients with moderate hepatic impairment. The dose should be doubled in these patients every 2 to 4 weeks until the target maintenance dose is reached, if tolerated by the patient.⁴

If the patient is being switched from an ACE inhibitor, the ACE inhibitor should be discontinued and the first dose of sacubitril/valsartan administered at least 36 hours after the last dose of the ACE inhibitor.⁴

No dosage adjustment is needed for patients with mild hepatic impairment or in those with mild or moderate renal impairment.⁴

For the treatment of hypertension (not an approved indication), daily sacubitril 49 mg/valsartan 51 mg did not significantly affect blood pressure beyond the reduction achieved with valsartan 80 mg; therefore, the daily dose may be sacubitril 97 mg/valsartan 103 mg once daily.^{5,6}

PRODUCT AVAILABILITY

Sacubitril/valsartan was approved for the treatment of heart failure on July 7, 2015.^{1,2} The product is available as an unscored, ovaloid, film-coated tablet in 3 different strengths (sacubitril 24 mg/valsartan 26 mg, sacubitril 49 mg/valsartan 51 mg, and sacubitril 97 mg/valsartan 103 mg) in bottles containing 60 or 180 tablets and blister packages of 100.⁴

The tablets should be stored in their original packaging and protected from moisture at 25°C (77°F), with excursions permitted between 15°C and 30°C (59°F and 86°F).⁴

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)

No REMS is required for sacubitril/valsartan.³

CONCLUSION

Sacubitril/valsartan is a new drug combination classified by the US Food and Drug Administration as a new molecular entity for the treatment of chronic heart failure. It was shown to reduce the rate of hospitalization in patients with heart failure (NNT, 35.7), mortality from cardiovascular causes (NNT, 31.3), and the combination of the 2 (NNT, 21.3). Rates of adverse events with sacubitril/valsartan are similar to those observed in patients treated with enalapril, with potential increased rates of hypotension; however, patients in the pivotal trial were pretreated with both sacubitril/valsartan and enalapril in order to eliminate patients who could not tolerate either drug. The adverse effects of valsartan are well known, but the long-term safety of sacubitril is unknown. Common criticisms of the pivotal PARADIGM-HF trial include the chosen dose of enalapril 10 mg twice daily, although guidelines delineate the dose of enalapril used across trials averaged 16.6 mg/day, and it is similar to the dose used in the SOLVD-Treatment trial. Head-to-head trials show synergistic reduction in blood pressure with sacubitril/valsartan compared with valsartan alone. Ongoing trials compare sacubitril/valsartan to olmesartan for the treatment of hypertension. Drug-drug interactions may occur with dual renin-angiotensin system blockers (avoid using with ACE inhibitors or other ARBs, and aliskiren should be avoided in patients with diabetes), potassium-sparing diuretics (may result in hyperkalemia), NSAIDs (the risk of renal impairment may be increased), and lithium (may increase lithium levels and the risk of lithium toxicity). No clinically important drug interactions were observed with other drugs commonly used for the treatment of patients with heart failure.

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Continuing Education Case Study Quiz

Goal—The goal of this activity is to educate pharmacists about the use of sacubitril/valsartan in the treatment of patients with chronic heart failure.

Objectives—At the completion of this activity, the reader will be able to:

1. Describe the pharmacology and pharmacokinetics of sacubitril/valsartan.
2. Discuss the risks associated with the use of sacubitril/valsartan.
3. Discuss the potential benefit of sacubitril/valsartan for an individual patient.
4. Apply the information on the use of sacubitril/valsartan to a case study.

Key Words—sacubitril/valsartan, chronic heart failure, new drugs

This CE activity is jointly provided by ProCE, Inc. and *Hospital Pharmacy*. ProCE, Inc. is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. ACPE Universal Activity Number 0221-9999-15-272-H01-P has been assigned to this knowledge-based home-study CE activity (initial release date 12-01-2015). This CE activity is approved for 1.5 contact hours (0.15 CEUs) in states that recognize ACPE providers. This CE activity is provided at no cost to participants. Completion of the evaluation and the post-test with a score of 70% or higher are required to receive CE credit. No partial credit will be given.

Faculty: *Dennis J. Cada, PharmD, FASHP, FASCP (Editor)*, Founder and Contributing Editor, *The Formulary*; *Danial E. Baker, PharmD, FASHP, FASCP*, Director, Drug Information Center, and Professor of Pharmacy Practice, College of Pharmacy, Washington State University; and *James Leonard*, Drug Information Intern, College of Pharmacy, Washington State University. The authors indicate no relationships that could be perceived as a conflict of interest. This activity is self-funded by *Hospital Pharmacy*.

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1. Sacubitril/valsartan is US Food and Drug Administration (FDA)–approved for the treatment of patients with chronic heart failure:
 - A. And preserved ejection fraction.
 - B. In conjunction with other therapies including diuretics, beta-blockers, and angiotensin converting enzyme (ACE) inhibitors.
 - C. In New York Heart Association (NYHA) classes I-IV.
 - D. To reduce the risk of cardiovascular death and hospitalization for heart failure.
2. Sacubitril is best described as a:
 - A. Neprilysin analogue.
 - B. Neprilysin inhibitor.
 - C. Prodrug of the neprilysin analogue LBQ657.
 - D. Prodrug of the neprilysin inhibitor LBQ657.
3. Which of the following best describes the metabolism and elimination of sacubitril?
 - A. It is converted to an active compound by CYP2C9, then eliminated renally.

- B. It is converted to an active compound by esterases, then eliminated without further change in the urine and feces.
 - C. It is excreted unchanged in the urine and feces.
 - D. It is extensively metabolized and eliminated renally.
4. Upon initiation of sacubitril/valsartan therapy, administered twice daily, steady-state concentrations are achieved within:
 - A. 2 days.
 - B. 3 days.
 - C. 7 days.
 - D. 2 weeks.
5. Which of the following is a caution associated with sacubitril/valsartan?
 - A. Cough
 - B. Hypokalemia
 - C. Hypotension
 - D. Hypertension
6. Which of the following parameters should be monitored in patients receiving sacubitril/valsartan therapy?
 - A. Blood pressure, hepatic function, and complete blood count
 - B. Blood pressure, kidney function, and serum electrolytes
 - C. NYHA class, kidney function, and pulmonary function
 - D. NYHA class, serum electrolytes, and hepatic function
7. Which of the following is a contraindication to use of sacubitril/valsartan?
 - A. Concomitant administration of lisinopril
 - B. Concomitant administration of warfarin
 - C. History of angioedema with an insect bite
 - D. History of rash with candesartan
8. Sacubitril/valsartan has a potential for a clinically significant drug-drug interaction with which of the following medications?
 - A. Acetaminophen
 - B. Furosemide
 - C. Lithium
 - D. Metoprolol

Case History

P.J. is a 66-year-old male patient with no known drug allergies. He has hypertension and hypercholesterolemia and developed chronic heart failure following a myocardial infarction 5 years ago. His current medications include furosemide 40 mg once daily, lisinopril 40 mg once daily, carvedilol 25 mg twice daily, atorvastatin 40 mg once daily, and aspirin 81 mg once daily. He has mild renal impairment and normal hepatic function. He was hospitalized twice this year for heart failure. His cardiologist has prescribed sacubitril/valsartan.

9. What is the recommended initial dose of sacubitril/valsartan for P.J.?
 - A. Sacubitril 24 mg/valsartan 26 mg twice daily
 - B. Sacubitril 49 mg/valsartan 51 mg once daily
 - C. Sacubitril 49 mg/valsartan 51 mg twice daily
 - D. Sacubitril 97 mg/valsartan 103 mg twice daily
10. When should sacubitril/valsartan therapy be initiated in P.J.?
 - A. Immediately
 - B. No sooner than 36 hours after he takes his last dose of lisinopril
 - C. One week after discontinuation of carvedilol
 - D. During his next hospitalization
11. Which of the following would be the recommended starting dose if P.J. were not receiving lisinopril?
 - A. Sacubitril 24 mg/valsartan 26 mg twice daily
 - B. Sacubitril 49 mg/valsartan 51 mg once daily
 - C. Sacubitril 49 mg/valsartan 51 mg twice daily
 - D. Sacubitril 97 mg/valsartan 103 mg twice daily
12. How soon should the sacubitril/valsartan dose be increased?
 - A. 3 to 5 days
 - B. 1 to 2 weeks
 - C. 2 to 4 weeks
 - D. A dose increase is not recommended for P.J.; his initial dose was the target maintenance dose.
13. What is the target dose of sacubitril/valsartan for P.J., if tolerated?
 - A. Sacubitril 24 mg/valsartan 26 mg twice daily
 - B. Sacubitril 49 mg/valsartan 51 mg once daily
 - C. Sacubitril 49 mg/valsartan 51 mg twice daily
 - D. Sacubitril 97 mg/valsartan 103 mg twice daily

14. The side effects most commonly reported in patients treated with sacubitril/valsartan are:
- A. Diarrhea, hypertension, fatigue, and dizziness.
 - B. Hypertension, hypokalemia, cough, and dizziness.
 - C. Hypotension, hyperkalemia, cough, and dizziness.
 - D. Nausea, vomiting, diarrhea, and headache.
15. Which of the following patients is NOT a candidate for sacubitril/valsartan therapy?
- A. A 72-year old male hospitalized with previously untreated NYHA class II heart failure and reduced ejection fraction
 - B. A 55-year old male with NYHA class III heart failure, reduced ejection fraction, and a history of angioedema with enalapril
 - C. A 35-year old female with NYHA class IV heart failure, reduced ejection fraction, and a history of therapy with valsartan
 - D. A 65-year old male with NYHA class III heart failure, reduced ejection fraction, and a history of therapy with ramipril ■