Sacubitril and Valsartan (ENTRESTO™)
Criteria for Use
September 2015
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.**

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at http://www.pbm.va.gov *or* https://vaww.cmopnational.va.gov/cmop/PBM/default.aspx *for further information.*

Exclusion Criteria *If the answer to ANY item below is met, then the patient should NOT receive sacubitril/valsartan*

- ☐ Current acute decompensated heart failure (refers to initial therapy only)
- ☐ Hypersensitivity to any component of sacubitril/valsartan
- ☐ History of angioedema related to an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB)
- ☐ History of intolerable side effects to an ARB
- ☐ Concomitant treatment with aliskiren in patients with diabetes
- ☐ Need for continued therapy with an ACEI, ARB alone, or direct renin inhibitor (aliskiren)
- ☐ Symptomatic hypotension
- ☐ Systolic blood pressure (SBP) < 100 mm Hg
- ☐ Severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 ml/min/1.73m^2) (Refer to Issues for Consideration)
- ☐ Severe hepatic impairment (Child-Pugh C) (Refer to Issues for Consideration)
- ☐ Serum potassium > 5.2 mEq/L
- ☐ History of non-adherence to guideline directed medical therapy for heart failure despite counseling (< 80% medication possession ratio)
- ☐ Pregnancy (i.e., known pregnancy or positive pregnancy test) (Refer to Inclusion Criteria and Monitoring)

Inclusion Criteria *The answers to all of the following must be fulfilled in order to meet criteria.*

- ☐ Restricted to VA Cardiology for initial prescription (Refer to Issues for Consideration)
- ☐ New York Heart Association (NYHA) Class II-IV heart failure symptoms (Refer to Issues for Consideration)
- ☐ Left ventricular ejection fraction (LVEF) ≤ 35% (Refer to Issues for Consideration)
- ☐ Most recent (while on therapeutic, or maximally tolerated, doses of evidence-based recommended medications for heart failure, as indicated) B-type natriuretic peptide (BNP) ≥ 150 pg/ml (or N-terminal pro-BNP [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
- ☐ Receiving a stable dose (i.e., ≥ 4 weeks) of a beta-blocker (after titration to maximally tolerated target dose as recommended by clinical practice guidelines), or documented intolerance or contraindication to a beta-blocker
- ☐ Receiving a stable dose (i.e., ≥ 4 weeks) of an ACEI or ARB (after titration to maximally tolerated target dose as recommended by clinical practice guidelines, and equivalent to at least enalapril 10 mg per day) Note: if sacubitril/valsartan is prescribed, other ACEI or ARB will need to be discontinued (Refer to Dosage and Administration, and Issues for Consideration)

For women of childbearing potential,

- □ pregnancy should be excluded prior to receiving sacubitril/valsartan and the patient provided contraceptive counseling on potential risk vs. benefit of taking sacubitril/valsartan if patient were to become pregnant (Refer to Monitoring)

Dosage and Administration (Also Refer to Issues for Consideration)

- **Patients currently on an ACEI (equivalent to > enalapril 10 mg per day) or ARB (equivalent to > valsartan 160 mg per day):** Concomitant use of sacubitril/valsartan with an ACEI or ARB is contraindicated. **Patients being switched from an ACEI to sacubitril/valsartan should have their ACEI discontinued for 36 hours prior to initiating sacubitril/valsartan** (patients being switched from an ARB do not require a wash-out period prior to starting therapy with 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 receiving lower doses of an ACEI (e.g., equivalent to enalapril ≤ 10 mg per day) or ARB (equivalent to valsartan ≤ 160 mg per day) despite attempts to titrate to a higher target dose:** 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. Treatment in these patients should be determined on a case by case basis.
- **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 as sacubitril/valsartan has not been studied in these patients.

Monitoring

- **Fetal Toxicity [Boxed Warning]:** there is the potential for sacubitril/valsartan to cause fetal harm if administered to a pregnant woman. Drugs that act on the renin-angiotensin-aldosterone system (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** was reported in 0.5% of patients treated with sacubitril/valsartan. 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. Black patients are at a higher risk of developing angioedema with sacubitril/valsartan (2.4%; vs. 0.5% with enalapril) compared to non-black patients (0.4%). 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** was reported as an adverse event in 18% of patients treated with sacubitril/valsartan. It is recommended to correct volume and/or salt-depletion prior to beginning therapy with sacubitril/valsartan, or start at a lower dose. If hypotension does occur, consider adjustment of medications that may contribute to hypotension, or reduce the dose of or discontinue sacubitril/valsartan, as indicated.
- **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 on sacubitril/valsartan. 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 (e.g., in PARADIGM-HF, safety monitoring criteria excluded patients if eGFR declined > 35% within 2 weeks after initiation of the study drug).
- **Hyperkalemia** may occur in patients treated with sacubitril/valsartan (reported in 12% of patients); monitor serum potassium periodically, especially in patients with risk factors for hyperkalemia (i.e., severe kidney impairment, diabetes, hypoaldosteronism, high potassium diet, receiving other medications that can increase potassium), with dose adjustments or discontinuation as indicated.
- **Drug Interactions**
  - *Dual (RAAS) blockade: ACEI* in combination with sacubitril/valsartan is contraindicated due to the risk for angioedema. Sacubitril/valsartan contains an *ARB*, therefore, use with an additional ARB should be avoided. Use of sacubitril/valsartan with *aliskiren* is contraindicated in patients with diabetes; also avoid concomitant use with aliskiren in patients with impaired kidney function (eGFR < 60 ml/min/1.73m2).
  - *Potassium-sparing diuretics, potassium supplements, or salt substitutes* containing potassium may increase serum potassium levels.
  - *Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) or selective Cyclooxygenase-2 Inhibitors (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. It should be noted that in general, these agents are not recommended in patients with heart failure given their association with increased morbidity and mortality.
  - *Lithium* in conjunction with an ARB has resulted in increased serum lithium concentrations and lithium toxicity; serum lithium levels should be monitored in patients treated with sacubitril/valsartan and lithium.
- **Adverse Event Reporting:** Providers should report any adverse reactions with sacubitril/valsartan by entering the information into CPRS' Allergies/ Adverse Reactions field and/or via local reporting mechanisms. Adverse events should also be reported, as appropriate, to the VA ADERS program and FDA MedWatch (1-800-FDA-1088, fax 1-800-FDA-0178, online at https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm, or by mail).

Issues for Consideration

- **FDA indications and usage:** to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic NYHA Class II to IV heart failure and reduced ejection fraction. Sacubitril/valsartan is usually used in patients receiving other therapies for heart failure, in place of an ACEI or other ARB.
- **NYHA Class II-IV HF:** Although sacubitril/valsartan is indicated in patients with NYHA Class II to IV HF, it is noted that only a small number (0.7%) of patients with NYHA Class IV HF were included in the pivotal study (PARADIGM-HF).
- **Local restrictions:** It is recommended that the patient be evaluated by Cardiology to obtain an initial prescription for sacubitril/valsartan, if feasible and deemed appropriate. Alternatively, sites may establish a mechanism for patients to be evaluated for an initial prescription by a designated provider(s) (e.g., primary care provider) with appropriate follow-up, monitoring, and titration (e.g., pharmacy titration clinic or follow-up by the PACT pharmacist).
- **Assessment of LVEF:** It is recommended that LVEF be assessed (e.g., by echocardiography, MUGA, CT scan, MRI, ventricular angiography) within the past 6 months (as per PARADIGM-HF) while on optimal, or maximally tolerated, doses of guideline directed medical therapy for heart failure. LVEF may be transiently reduced following acute coronary syndrome (ACS) and should be re-evaluated $\geq$ 3 months after the event. If the LVEF is found to be reduced either in the setting of a recent ACS or other secondary etiology that has resolved, repeat LVEF assessment should be conducted prior to considering sacubitril/valsartan.
- **ACEI target dose:** Maximum doses of enalapril for heart failure with reduced ejection fraction are 10 to 20 mg twice daily, based on target doses in clinical outcome trials. However, mean doses achieved in these trials were closer to 10 mg twice daily. How sacubitril/valsartan compares to a higher target dose of an ACEI (e.g., enalapril 20 mg twice daily) and whether there would be any additional benefit in switching these patients is unknown at this time; the risk vs. benefit of switching to sacubitril/valsartan or continuing present management at a higher target dose ACEI should be taken into consideration.
- **ACEI naïve patients:** 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. Although not studied in the pivotal outcome trial (PARADIGM-HF), the manufacturer recommends a starting dose of sacubitril/valsartan 24/26 mg twice daily in treatment naïve patients, doubling the dose every 2 to 4 weeks to the target maintenance dose of 97/103 mg twice daily, as tolerated.
- **Treatment with a mineralocorticoid receptor antagonist:** Prior to considering sacubitril/valsartan, a mineralocorticoid receptor antagonist may be a preferred treatment option based on the long-term outcome benefit in patients with heart failure with reduced ejection fraction. In addition, the majority of patients in the pivotal outcome trial (PARADIGM-HF) were being treated with this class of medication and considering treatment with a mineralocorticoid receptor antagonist was also part of the protocol for PARADIGM-HF.
- **Hydralazine/isosorbide dinitrate in black patients:** 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. This may also be considered a treatment option prior to sacubitril/valsartan, especially if angioedema is a concern in this patient population.
- **Renal and hepatic impairment:** Although the manufacturer's product information includes recommended dose adjustments (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) for patients with severe renal impairment (eGFR < 30 ml/min/1.73m^2) and moderate hepatic impairment (Child-Pugh B), these patients were not included in PARADIGM-HF (e.g., aspartate aminotransferase or alanine aminotransferase > 2 times the upper limit of normal excluded) and the safety of treatment with sacubitril/valsartan for the approved indication in this patient population is unknown at this time. If sacubitril/valsartan is prescribed in patients with severe renal impairment or moderate hepatic impairment, it should only be done after careful consideration of risk vs. benefit, and with close monitoring and follow-up.

Prepared: July 2015. Contact: Elaine Furmaga, PharmD, VA National Pharmacy Benefits Management Services