Sacubitril/valsartan (Entresto) is a combination of a neprilysin inhibitor and an angiotensin receptor blocker (ARB). It is labeled for use to reduce the risk of cardiovascular death and the rate of hospitalization in patients with chronic heart failure (New York Heart Association [NYHA] class II to IV) and reduced ejection fraction.1

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Dose form</th>
<th>Cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sacubitril/valsartan (Entresto)</td>
<td>49/51 mg twice daily to start, increasing to 97/103 mg twice daily after two to four weeks if tolerated</td>
<td>24/26-, 49/51-, and 97/103-mg tablets</td>
<td>$413</td>
</tr>
</tbody>
</table>


SAFETY

The most significant adverse effects of sacubitril/valsartan are symptomatic hypotension, renal dysfunction, and hyperkalemia. Clinically relevant hypotension will occur in about 18% of patients taking sacubitril/valsartan vs. 12% of those taking enalapril (Vasotec; number needed to treat to harm = 17). Approximately 3% of patients will develop an elevated creatinine level (greater than 2.5 mg per dL [221 µmol per L]), compared with 4.5% of patients receiving enalapril. Hyperkalemia (serum potassium concentration greater than 5.5 mEq per L [5.5 mmol per L]) will occur in approximately 16% of patients, a rate similar to that of enalapril,1,2 and it is more likely in patients treated with other potassium-sparing diuretics. Angioedema occurs infrequently and at about the same rate as in patients treated with angiotensin-converting enzyme (ACE) inhibitors. Sacubitril/valsartan should not be used in patients with a history of angioedema related to previous ACE inhibitor or ARB therapy. Sacubitril/valsartan can cause fetal harm when administered to pregnant women and should not be used in patients who are breastfeeding.

TOLERABILITY

Sacubitril/valsartan is generally well tolerated by most patients. Approximately 11% of patients will discontinue therapy because of adverse effects.1,2 It should not be used together with an ACE inhibitor because of the increased risk of angioedema, with another ARB, or with aliskiren (Tekturna) in patients with diabetes mellitus. Sacubitril/valsartan therapy may increase serum lithium concentrations in patients taking lithium.

EFFECTIVENESS

Sacubitril/valsartan reduces the risk of death and the rate of hospitalization in patients with heart failure.2 Researchers compared treatment with sacubitril/valsartan vs. enalapril in a study of 8,399 patients, most of whom had NYHA class III or IV heart failure, who were also being treated with a beta blocker and a mineralocorticoid antagonist. Mortality rates from a cardiovascular cause over 3.5 years were 16.5% with enalapril vs. 13.3% with sacubitril/valsartan (number needed to treat [NNT] for 3.5 years = 31; 95% confidence interval [CI], 22 to 62). Sacubitril/valsartan also decreased the rate
of first hospitalization for heart failure over a 3.5-year period (15.6% with enalapril vs. 12.8% with sacubitril/valsartan; NNT for 3.5 years = 36; 95% CI, 23 to 77).²

The average dose of enalapril used in this study was 18.9 mg, and the average dose of sacubitril/valsartan was 375 mg (the equivalent of approximately 300 mg of valsartan). The doses of enalapril and valsartan were consistent with those used in previous clinical trials that have demonstrated mortality reduction in patients with heart failure. However, the dose of enalapril used was not the maximum, whereas the dose of valsartan was. This is a potential straw man bias in which a drug is compared to a suboptimal comparator and could overestimate the relative benefit.

**PRICE**

The cost of a one-month supply of sacubitril/valsartan is approximately $413. In comparison, an ACE inhibitor such as enalapril costs $20 ($770 for Vasotec), and an ARB such as valsartan (Diovan) costs $18 ($214). Sacubitril/valsartan is on the Medicare part D formulary but may not be covered by all insurance plans.

**SIMPPLICITY**

The recommended starting dosage of sacubitril/valsartan is 49/51 mg twice daily. The starting dosage should be reduced to 24/26 mg twice daily for patients not currently taking an ACE inhibitor or an ARB, or who were previously taking low doses of these agents, as well as for patients with severe renal impairment or moderate hepatic impairment. If the initial dosage is tolerated, it should be doubled after two to four weeks to the target maintenance dosage of 97/103 mg twice daily.

When switching from an ACE inhibitor to sacubitril/valsartan, allow a washout period of 36 hours between the two treatments. The washout period is not needed when switching from an ARB to sacubitril/valsartan. Monitor serum potassium levels periodically and treat appropriately, especially in patients with risk factors for hyperkalemia such as severe renal impairment, diabetes, hypoadosteronism, or a high-potassium diet. Closely monitor serum creatinine levels, and lower the dosage or stop therapy in patients who develop a clinically significant decrease in renal function.

**Bottom Line**

Sacubitril/valsartan provides a small mortality benefit and decreases heart failure–related hospitalizations over and above an ACE inhibitor. It may be used in place of an ACE inhibitor in patients receiving optimal doses of guideline-directed medical therapy that includes ACE inhibitors, beta blockers, and aldosterone antagonists. Sacubitril/valsartan is much more expensive than other ACE inhibitor or ARB treatment options. When switching from an ACE inhibitor, patients should wait 36 hours before starting sacubitril/valsartan.

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**REFERENCES**
