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IN BRIEF

Sacubitril/Valsartan (*Entresto*) Expanded Indication

The oral fixed-dose combination of the neprilysin inhibitor sacubitril and the angiotensin receptor blocker (ARB) valsartan (*Entresto* – Novartis) was approved by the FDA in 2015 to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction (HFrEF; LVEF <40%).¹ The indication has now been expanded to include patients with chronic heart failure with any LVEF; the label specifies that benefits are most clearly evident in patients with LVEF below normal. *Entresto* is the first drug to be approved in the US for this indication.

TYPES OF HF – Almost half of all patients with heart failure have HFrEF, almost half have heart failure with preserved ejection fraction (HFpEF; LVEF ≥50%), and the rest have heart failure with mid-range ejection fraction (HFmrEF; LVEF 41-49%).

CLINICAL STUDY – FDA approval of the expanded indication for *Entresto* was based on the results of a double-blind trial (PARAGON-HF) in 4822 patients with NYHA class II-IV heart failure, LVEF ≥45%, elevated levels of natriuretic peptides, and structural heart disease. The primary endpoint was a composite of total hospitalizations for heart failure and cardiovascular death. After a median follow-up of 35 months, there were 894 primary events in 526 patients randomized to receive sacubitril/valsartan 97/103 mg twice daily

and 1009 primary events in 557 patients randomized to receive valsartan 160 mg twice daily (RR 0.87; 95% CI 0.75-1.01).² Although statistical significance was narrowly missed, subgroup analyses suggested that sacubitril/valsartan showed benefit in patients with LVEF 45-57% and in women.

DOSAGE – The recommended starting dosage of sacubitril/valsartan in adults is 49/51 mg twice daily. The dose should be doubled every 2-4 weeks as tolerated to reach a final dose of 97/103 mg. ACE inhibitor treatment should be discontinued 36 hours before starting *Entresto*. In patients who had not been taking an ACE inhibitor or an ARB, or in those with severe renal impairment (eGFR <30 mL/min/1.73 m²) or moderate hepatic impairment, the recommended starting dosage of *Entresto* is 24/26 mg twice daily. *Entresto* is not recommended for patients with severe hepatic impairment. One month's treatment at the target dosage costs \$583.00.³ ■

Additional Content Available Online

Comparison Table: Some Drugs for HFrEF
<http://medicalletter.org/TML-article-1619e>

1. Sacubitril/valsartan (*Entresto*) for heart failure. *Med Lett Drugs Ther* 2015; 57:107.
2. SD Solomon et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med* 2019; 381:1609.
3. Approximate WAC. WAC = wholesale acquisition cost, or manufacturer's published price to wholesalers; WAC represents published catalogue or list prices and may not represent actual transactional prices. Source: Analysource® Monthly. April 5, 2021. Reprinted with permission by First Databank, Inc. All rights reserved. ©2021. www.fdbhealth.com/policies/drug-pricing-policy.

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