FDA Approves First-in-Class Combo Drug for Heart Failure

BY JUDITH M. ORVOS, ELS

A pill combining valsartan and sacubitril has received first-in-class approval for heart failure under the Food and Drug Administration's priority review program. Entresto offers practitioners a new option for reducing risk of cardiovascular death and hospitalization in patients with NYHA class II-IV heart failure and reduced ejection fraction.

Previously known as LCZ696, Entresto (Novartis) is an angiotension receptor-neprilysin inhibitor that exerts effects on and beyond the renin-angiotensin system. It is the only treatment to show a significant mortality benefit in a head-to-head trial against the angiotensin-converting enzyme (ACE) inhibitor enalapril. The FDA approval was based on results from the PARADIGM-HF (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) randomized clinical trial, which were presented at the European Society of Cardiology 2014 Congress in Barcelona, Spain.

More than 8,000 adults with class II, III, or IV heart failure and an ejection fraction of 40% or less were enrolled in PARADIGM-HF. Most of them were also receiving currently approved heart failure treatments, such as beta-blockers, diuretics, and mineralocorticoid antagonists. Compared with enalapril, the combination pill was found to reduce risk of death from cardiovascular causes by 20%, risk of heart failure hospitalizations by 21%, and risk of all-cause mortality by 16%. Statistically significant decreases in symptoms and physical limitations of heart failure were also reported. The trial was stopped early at median follow-up of 27 months because an overwhelming benefit for the combination pill was found. Death from cardiovascular causes occurred in 914 (21.8%) of patients taking the combination drug compared with 1,117 (26.5%) in the enalapril group.

Cardiologist Javed Butler, MD, MPH, co-director of the Heart Institute at Stony Brook University in Stony Brook, NY, said he found it encouraging that all of the subgroups studied in PARADIGM-HF showed benefit from receiving the combination pill. "In the absence of a specific trial in long-term care facility residents," said Dr. Butler, "we would have to assume that the drug would work in that population."

Jeffrey Nichols, MD, CMD, vice president of Home Care Services at Cabrini Eldercare in Dobbs Ferry, NY, felt that $400 per month that the company is likely to be charging for this "first-in-class" medication may give LTC facilities pause. "Nursing homes that manage post-acute heart failure patients will be torn over its use when evidence suggests marginal or unknown effectiveness, and its impact on long-stay residents will be minimal," he said. Dr. Nichols also noted that Entresto is primarily used for systolic heart failure, whereas the majority of residents in skilled nursing facilities with failing hearts have primarily diastolic dysfunction.

Analysis of safety data from PARADIGM-HF showed that the combination pill had a tolerability profile similar to that for enalapril. The most common adverse effects in the individuals taking it were hypotension, seen in 588 (14%) patients vs. 388 (9.2%) in the enalapril group, and elevations in levels of serum creatinine and potassium. Differences between the two groups for the latter two adverse events did not rise to statistical significance. Falls were reported in 1.9% of the group taking the combination pill vs. 1.3% of the patients treated with enalapril. Angioedema also was reported with the combination pill and the risk was higher in black patients (2.4% vs. 0.5%) and in patients with a prior history of angioedema.

Practitioners should be aware that Entresto should not be taken with any drug from the ACE inhibitor class because of the increased risk of angioedema. When switching patients on ACE inhibitors to Entresto, a 36-hour washout period between the administration of drugs is required. Dr. Nichols said he believes it is likely that some SNF residents who are taking enalapril or another ACE inhibitor may be switched to Entresto for the presumed benefit in fewer deaths that was associated with the drug in initial trials.

The recommended starting dose of Entresto is 49/51 mg twice daily and it is typically given in conjunction with other heart failure therapies in place of an ACE inhibitor or an angiotensin II receptor blocker (ARB). For patients with limited renal function or who are taking other drugs to control blood pressure, Dr. Butler suggested starting with half the dose and titrating upward. In some individuals with a low ejection fraction, he said, use of Entresto may make it possible to reduce the dosage of or eliminate medication for high blood pressure.

The tolerability and safety of uptitrating Entresto from an initial dose of 50 mg twice daily to a target dose of 200 mg twice daily was studied in TITRATION. A broader range of patients were enrolled in that randomized, double-blind trial than in PARADIGM-HF, including inpatients and individuals who had not taken ACE inhibitors or ARBs. More than 70% of the 429 patients who completed the study, which was open-label, achieved the target dose of 200 mg twice daily over a 3- or 6-week uptitration regimen.

Dr. Butler is on the steering committee for Novartis's pharmacovigilance registry.

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