



Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: Novel Heart Failure Drug Therapies
-May 2017-



Background:

The IHS National Pharmacy & Therapeutics Committee (NPTC) discussed the novel heart failure drug therapies, sacubitril/valsartan and ivabradine, at the May 2017 meeting. The NPTC last reviewed heart failure pharmacotherapies in February 2009 at which time neither novel heart failure drug was FDA-approved. After discussing the clinical and pharmacoeconomic data, along with IHS procurement and utilization trends, **no changes were made to the National Core Formulary (NCF).**

Heart failure is a structural and/or functional abnormality that leads to decreased cardiac output and/or increased intracardiac pressures. Diseases such as coronary heart disease, hypertension and diabetes increase the risk of heart failure, as do factors such as smoking, a high fat diet, sedentary lifestyle and obesity (CDC 2016, Ponikowski 2016). Heart failure patients experience symptoms such as shortness of breath upon exertion or at rest, fatigue, weakness, and edema of the lower extremities (Mayo Clinic 2017). It affects approximately 5.7 million people in the United States, and the total nationwide cost for heart failure care in 2013 was over \$30 billion (CDC 2016, Mizacci 2017). As heart failure progresses, patients may experience reduced functional capacity, decreased quality of life, depression, complications and hospitalizations (Mizacci 2017, Mayo Clinic 2017). Approximately one-half of patients diagnosed with heart failure die within 5 years of diagnosis. The goals of treatment are to address the underlying cause, decrease symptoms, prolong survival, improve quality of life and slow disease progression (Mizacci 2017, NHLBI 2017). Available treatment options include lifestyle changes, devices and procedures, and medications including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta blockers, aldosterone antagonists, hydralazine, isosorbide dinitrate, and diuretics, as well as two new classes of medications, angiotensin-receptor neprilysin inhibitors and I₁ channel blockers (AHA 2017, NHLBI 2017).

Discussion:

Sacubitril/valsartan is an angiotensin-receptor neprilysin inhibitor (ARNI) approved by the FDA for treatment of heart failure in 2015. Sacubitril inhibits neprilysin, a neutral endopeptidase that degrades natriuretic peptides, bradykinin and adrenomedullin. Inhibiting neprilysin increases the levels of these substances, as well as countering the neurohormonal over-activation which contributes to vasoconstriction, sodium retention and maladaptive remodeling. It increases plasma accumulation of atrial natriuretic peptide and B-type natriuretic peptide (BNP), leading to decreased preload, afterload and total body sodium and fluid composition (McMurray 2014). Valsartan is an ARB that works through the renin angiotensin system to decrease vasoconstriction, blood pressure, aldosterone, fibrosis and ventricular hypertrophy. The combination drug sacubitril/valsartan was evaluated in one trial, [PARADIGM-HF](#). This was a double-blind, randomized controlled trial (RCT) of patients with New York Heart Association (NYHA) heart failure Class II-IV symptoms and an initial ejection fraction (EF) ≤40%. For at least 4 weeks prior to screening, patients were required to take a stable dose of a beta-blocker and an ACE inhibitor (or ARB) equivalent to at least 10mg of enalapril daily. The 1st phase was a single-blind run-in period with all patients receiving enalapril for 2 weeks. The 2nd phase was a single-blind run-in period with all patients receiving sacubitril/valsartan for 4 to 6 weeks. In phase 3, subjects were randomly assigned to either enalapril 10mg BID or sacubitril/valsartan 200mg (Papadimitriou 2017). The primary outcome was a composite of death from cardiovascular causes or first hospitalization for heart failure. The trial was stopped early as the pre-specified stopping boundary for an overwhelming benefit had been reached. The mean duration of follow-up was 27 months, with a number needed to treat (NNT) to prevent one primary event of 21 and a NNT to prevent one death from cardiovascular cause of 32 (McMurray 2014). Several concerns were raised about the trial, including external validity, whether the efficacy was due to the combination regimen or the maximally-dosed valsartan, whether a higher comparison dose of enalapril would have been more appropriate, and whether author bias was a factor. The [PARAGON-HF](#) study comparing sacubitril/valsartan with valsartan is ongoing (anticipated completion date of March 2019) and may offer clarity of its benefit in patients with preserved EF (Chen 2016, Giberl¹ 2015).

Ivabradine is an I_f channel blocker which received FDA approval in 2015 to reduce hospitalization from worsening heart failure. It selectively and specifically inhibits the hyperpolarization-activated cyclic nucleotide-gated channels (f-channels) within the sinoatrial (SA) node of cardiac tissue, disrupting I_f ion current flow prolonging diastolic depolarization, slowing firing in the SA node and reducing heart rate. The [BEAUTIFUL trial](#) was a multi-centered, double blind, RCT comparing ivabradine to placebo in mostly males with NYHA Class II heart failure, many of whom had no heart failure symptoms. The primary endpoint considered was a composite of cardiovascular death, hospital admission for myocardial infarction (MI), or hospital admission for new-onset or worsening heart failure. The primary endpoint occurred in 15.4% of ivabradine patients and 15.3% on placebo (p=0.94). The [SHIFT trial](#) was a randomized, double blind, placebo-controlled, parallel-group study with a primary endpoint of a composite of cardiovascular death or hospital admission for worsening heart failure. The primary endpoint occurred in 24% of ivabradine patients and in 29% on placebo (p<0.0001). Cardiovascular deaths were not significantly reduced but deaths due to heart failure were decreased and all-cause hospital admissions were significantly lowered. The [SIGNIFY trial](#) was a double blind RCT of patients with coronary artery disease but without evidence of heart failure. The primary endpoint was a composite of nonfatal MI and multiple outcomes under the term “cardiovascular death”. Ivabradine was not found to reduce cardiovascular events in this population (Gibler² 2015, Swedbert 2010, Fox 2013).

In the [2016 update to the 2013 ACCF/AHA Guideline for the Management of Heart Failure](#), ARNIs were added to the “Recommendations for Renin-Angiotensin System Inhibition” at the same class of guideline recommendation (but at a lower level of evidence) as ACE inhibitors and ARBs. Ivabradine received a lower level of recommendation for benefit in reducing heart failure hospitalization for patients with symptomatic (NYHA class II-III), stable chronic heart failure with reduced ejection fraction (LVEF ≤ 35%) who are receiving guideline-directed evaluation and management, including a beta blocker at maximally tolerated dose, and who are in sinus rhythm with a heart rate of 70 beats per minute or greater at rest (Yancy 2016).

Findings:

Sacubitril/valsartan may decrease morbidity and mortality in patients with chronic symptomatic heart failure with a reduced ejection fraction, and ivabradine may reduce heart failure hospitalizations in patients with symptomatic stable chronic heart failure with a reduced ejection fraction. Based on these determinations, the NPTC declined to make changes to the NCF due to insufficient decisive evidence.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the [NPTC website](#).

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