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Drug Class Literature Scan: ACE Inhibitors, ARBs, Direct Renin Inhibitors and Sacubitril/Valsartan

Date of Review: May 2017

Date of Last Review: January and September 2015
Literature Search: 01/01/2015—03/01/2017

Current Status of PDL Class:
See **Appendix 1**.

Conclusions:

- Since the last review additional evidence has become available with the publication of 4 new guidelines,[1–4] 4 new systematic reviews and meta-analyses,[5–8] 1 randomized controlled trial,[9] 2 new formulations,[10,11] and 1 Food and Drug Administration (FDA) safety alert.[12]
- There is moderate quality evidence of no difference between angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) for total mortality, cardiovascular (CV) events, or CV mortality in patients with hypertension. Incidence of adverse effects was slightly lower for ARBs compared with ACEIs primarily due to a higher incidence of dry cough with ACEIs.[5]
- In patients with hypertension, moderate quality evidence demonstrates that compared with calcium channel blockers (CCBs), renin-angiotensin system (RAS) inhibitors reduce death or hospitalizations for heart failure (HF) (absolute risk reduction (ARR) 1.2%), increase fatal and non-fatal stroke (absolute risk increase (ARI) 0.7%) and are similar for all-cause death, total CV events and end stage renal failure (ESRF) events.[6]
- Moderate quality evidence reveals that compared with thiazides, RAS inhibitors increase hospitalizations for heart failure (ARI 1%) and increase fatal and non-fatal stroke (ARI 0.6%). RAS inhibitors are similar to thiazides for all-cause death, total CV events, fatal and non-fatal myocardial infarction (MI) and ESRF events.[6]
- Low quality evidence shows that compared with beta-blockers, RAS inhibitors reduce total CV events (ARR 1.7%) and fatal and non-fatal stroke (ARR 1.7%) and are similar for all-cause death, HF, and total MI.[6]
- Low to moderate quality evidence shows when ARBs were compared to placebo they did not produce statistically significant reductions in the risk of MI, heart failure (HF), hospitalization, or mortality.[7]
- Moderate quality evidence concluded the direct renin inhibitor (DRI), aliskiren, shows no benefit for the outcomes of major CV events, total mortality, cardiac death, MI, or stroke.[8]
- The FDA issued a warnings and precautions update regarding the possibility of sprue-like enteropathy associated with olmesartan use.[12]
- Guidelines recommend sacubitril/valsartan as an option for patients with the following characteristics:[2,3]
  - with New York Heart Association (NYHA) class II to IV HF symptoms and
  - with a left ventricular ejection fraction of 35% or less and
  - who are already taking a stable dose of ACEI or ARB

Recommendations:

- For ACEIs, ARBs and DRIs, no further review or research is needed at this time.
- After evaluation of comparative costs in executive session, no PDL changes are recommended.
- No changes to Entresto (sacubitril/valsartan) prior authorization (PA) criteria are recommended based on evidence review.

Previous Conclusions:

- There is moderate quality evidence of no difference between ACEI and ARBs in regards to reduction in mortality, CV mortality, hospitalizations or stroke, or progression to chronic kidney disease in patients with primary hypertension. There is insufficient evidence at this time to suggest DRIs offer any benefit in these clinically relevant outcomes.
- There is moderate quality evidence that risk of dry cough and angioedema associated with ACEIs is higher than with ARBs or DRIs. Incidence of angioedema is also more common in heart failure patients than other populations. However, angioedema remains a very rare adverse effect of ACEIs.
- There is moderate quality evidence that dual blockade of the RAS does not provide additional benefit in clinically relevant outcomes compared with monotherapy and increases risk of harm, specifically the risk of hyperkalemia, hypotension, renal failure and withdrawal due to adverse events.
- There is insufficient evidence that fixed combination drug formulations containing an ACEI, AIIRA or DRI offer additional benefit in clinically relevant outcomes compared to the respective free drug combination.
- Evidence for use of sacubitril/valsartan is limited to one 27-month clinical trial (n=8,399) with low and moderate risk of selection and performance bias, respectively. The study was composed of patients with stable, mildly symptomatic HFrEF (New York Heart Association [NYHA] Classes II and III) with a mean ejection fraction (EF) of 29%. Patients in the study remained on standard HF therapy (i.e., beta-blocker, diuretic(s), and aldosterone antagonist).
- There is low to moderate quality evidence that sacubitril/valsartan 97/103 mg twice daily (BID) can reduce risk of death from CV causes or hospitalization for HF by an absolute difference of 4.7% compared to enalapril 10 mg BID (21.8% vs. 26.5%, respectively; Hazard Ratio [HR]=0.80 (95% Confidence Interval [CI] 0.73-0.87; p<0.001; number needed-to-treat [NNT] 22).
- There is low quality evidence, based on a secondary endpoint, that sacubitril/valsartan may reduce all-cause mortality, driven almost entirely by reduction in CV mortality, by an absolute difference of 2.8% compared to enalapril (17.0% vs. 19.8%, respectively; HR=0.84 (95% CI, 0.76-0.93; p<0.001; NNT 36).
- There is low quality evidence that sacubitril/valsartan may not reduce perceived quality of life and health status versus enalapril when assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ). The difference in KCCQ scores were statistically significant when assessed at 8 months (a difference of 1.61 points on a 100-point scale), but a much larger difference is needed to be clinically meaningful.
- There is insufficient evidence to determine if the results seen were driven by the maximum daily dose of valsartan (320 mg) or by the addition of the neprilysin inhibitor sacubitril to maximally dosed valsartan. Additional studies will help guide place in therapy for sacubitril/valsartan in the management of HFrEF, including whether a neprilysin inhibitor with an ARB will replace an ACE-I or ARB in most HFrEF patients.
- Safety data are limited to the one trial. There is low quality evidence that sacubitril/valsartan may be tolerated similarly as enalapril, but sacubitril/valsartan was associated with more episodes of symptomatic hypotension than enalapril (14.0% vs. 9.2%, respectively). Enalapril was associated higher incidence of cough than sacubitril/valsartan (14.3% vs. 11.3%, respectively) and higher incidence of hyperkalemia >6.0 mEq/L (5.6% vs. 4.3%, respectively).
- Based on study methodology, there is insufficient evidence of a dose-response for sacubitril/valsartan, and a daily dose of 400 mg is needed to expect the mortality and morbidity benefits demonstrated in the trial.
- Based on the population studied, there is insufficient evidence for the use of sacubitril/valsartan in the following populations: NYHA class I or IV, HF patients with preserved EF, pediatric populations, very elderly populations, patients with refractory hypertension or marginally low blood pressure, or ACEI-naïve patients. Blacks were also underrepresented in this trial despite the high prevalence of HF and higher incidence of angioedema in this population.

Previous Recommendations:

- For ACEIs, ARBs and DRIs, no further review or research is needed at this time. After review of costs in the executive session, no changes to the PDL recommended.
- Restrict use of sacubitril/valsartan to populations where it has demonstrated efficacy.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

ACEIs versus angiotensin receptor blockers ARBs for primary hypertension

A 2014 Cochrane review compared the effects of ACEIs and ARBs on total mortality and CV events, and the rates of withdrawals due to adverse effects in patients with primary hypertension.[5] Studies included in this systematic review were randomized controlled trials (RCTs) comparing ACEI versus ARB lasting greater than one year in patients with uncontrolled or controlled primary hypertension. Hypertension was defined as systolic blood pressure (SBP) > 140 mm Hg or a diastolic blood pressure (DBP) > 90 mm Hg or both at baseline. The ACEIs included in the analysis were: enalapril, ramipril, fosinopril, quinapril and lisinopril. Telmisartan, losartan, candesartan, irbesartan, and valsartan were the ARBs that were studied in the RCTs. Nine trials with 11,007 subjects met inclusion criteria. Five trials reported on total mortality, 3 reported on total CV events, and 4 reported on CV mortality. Eight trials had data on adverse effects and safety. Studies were of good to moderate quality with minimal risk of bias. There was no evidence of a difference between ACEIs and ARBs for total mortality (risk ratio (RR) 0.98; 95% confidence interval (CI) 0.88 to 1.10), total CV events (RR 1.07; 95% CI 0.96 to 1.1 9), or CV mortality (RR 0.98; 95% CI 0.85 to 1.13).[5] Incidence of adverse effects was slightly lower for ARBs compared with ACEIs (RR 0.83; 95% CI 0.74 to 0.93; ARR 1.8%, NNTB 55 over 4.1 years), primarily due to a higher incidence of dry cough with ACEIs.[5] Forty three percent of adverse events in the ACEI patients were due to cough compared to 4% in the ARB arms.[5] Other adverse effects associated with ACEIs included atrial flutter, edema, rash, and rise in creatinine.[5] Adverse effects prompting withdrawal of ARB therapy included dizziness, hypotension, palpitations, dyspnea, headache, nausea, edema, urticaria and macroalbuminuria.[5]

First-line drugs inhibiting renin-aldosterone system (RAS) versus other first-line antihypertensive drug classes for hypertension

The purpose of a 2015 Cochrane review was to evaluate efficacy of RAS inhibitors compared to other first line antihypertensive agents.[6] The population of interest was patients with primary hypertension (≥ 130/85 mm Hg). A blood pressure less than the standard 140/90 mm Hg was selected to include more patients including diabetics, who have a lower target threshold for blood pressure control. RCTs had to have at least 6 months of follow-up data for inclusion in

the review. RAS inhibitors included ACEIs, ARBs, and renin inhibitors. ACEI available in the United States (U.S.) that were evaluated in the trials included benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril. The ARBs marketed in the U.S. included candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan. The two renin inhibitors were aliskiren and remikiren. Only aliskiren is available in the U.S. Comparators included thiazide diuretics, beta blockers, and CCBs. Primary outcomes were all-cause mortality, fatal and non-fatal stroke, fatal and non-fatal myocardial infarction (MI), fatal and non-fatal HF requiring hospitalization, total CV events and ESRF.[6] Forty two studies met inclusion criteria involving 65,733 subjects with a mean age of 66 years. The CCB and thiazide studies were rated as moderate to high quality by the reviewers. The beta blocker studies were evaluated as low quality due to insufficient details regarding methods of blinding, allocation of concealment and randomization, or incomplete reporting of outcome data.[6] Over half of all the studies included in this review were completed in Europe.

Comparator CCBs included amlodipine, nifedipine, diltiazem, felodipine, and verapamil. Compared with CCBs moderate quality evidence showed that RAS inhibitors decreased HF (RR 0.83, 95% CI 0.77 to 0.90), but they increased stroke (RR 1.19, 95% CI 1.08 to 1.32).[6] CCBs and RAS inhibitors had similar effects on all-cause death (RR 1.03, 95% CI 0.98 to 1.09), total CV events, (RR 0.98, 95% CI 0.93 to 1.02), total MI (RR 1.01, 95% CI 0.93 to 1.09), and ESRF (RR 0.88, 95% CI 0.74 to 1.05).[6]

Thiazides included in the studies were chlorthalidone and hydrochlorothiazide. Compared with thiazides, moderate quality evidence revealed that RAS inhibitors increased HF (RR 1.19, 95% CI 1.07 to 1.31), and increased stroke (RR 1.14, 95% CI 1.02 to 1.28).[6] They had similar effects on all-cause death (RR 1.00, 95% CI 0.94 to 1.07), total CV events (RR 1.05, 95% CI 1.00 to 1.11), total MI (RR 0.93, 95% CI 0.86 to 1.01), and ESRF (RR 1.10, 95% CI 0.88 to 1.37).[6]

Beta blockers included atenolol, carvedilol, metoprolol, bisoprolol, and acebutolol. Compared with beta-blockers, low quality evidence demonstrated that RAS inhibitors decreased total CV events (RR 0.88, 95% CI 0.80 to 0.98), and decreased stroke (RR 0.75, 95% CI 0.63 to 0.88).[6] No significant differences were noted between RAS inhibitors and beta-blockers for all-cause death (RR 0.89, 95% CI 0.78 to 1.01), HF (RR 0.95, 95% CI 0.76 to 1.18), and total MI (RR 1.05, 95% CI 0.86 to 1.27)[6] The effect on ESRD could not be assessed due to insufficient data.

In summary, compared with CCBs, RAS inhibitors reduce death or hospitalizations for HF (absolute risk reduction (ARR) 1.2%), increase fatal and non-fatal stroke (absolute risk increase (ARI) 0.7%) and are similar for all-cause death, total CV events and ESRF events. Compared with thiazides, RAS inhibitors increase hospitalizations for HF (ARI 1%) and increase fatal and non-fatal stroke (ARI 0.6%). RAS inhibitors are similar to thiazides for all-cause death, total CV events fatal and non-fatal MI and ESRF events. Compared with beta-blockers, RAS inhibitors reduce total CV events (ARR 1.7%) and fatal and non-fatal stroke (ARR 1.7%) and are similar for all-cause death, HF, and total MI.

Cardiovascular and cerebrovascular outcomes of long-term angiotensin receptor blockade in essential hypertension

The purpose of this systematic review and meta-analysis was to assess the long-term effects of ARBs on blood pressure (BP) control, MI, hospitalization for HF, cerebrovascular events, CV mortality, and all-cause mortality.[7] Hypertension trials were included if they reported on ARB efficacy in either BP control (relative to placebo for periods ≥6 months) or cardiovascular/cerebrovascular outcomes (relative to non-ARB antihypertensive therapies for periods ≥24 months).[7] A total of 7 articles were included in the analysis with a total of 16,864 subjects. Studies were rated as low to moderate quality due to insufficient reporting of study methodology or selective outcome reporting.[7] Six ARB agents were studied: candesartan, eprosartan, irbesartan, olmesartan, losartan and telmisartan. ARB therapy significantly reduced mean systolic BP (weighted mean difference (WMD) −4.86; 95% CI: −6.19 to −3.53 mm Hg) and diastolic BP (WMD: −2.75; 95% CI: −3.65 to −1.86 mm Hg] compared to placebo.[7] The risk of stroke was reduced by 21% in the ARB group compared with alternative antihypertensives (RR: 0.79; 95% CI: 0.66 to 0.96).[7] ARBs did not produce statistically significant reductions in the risk of MI, HF hospitalization, or mortality. The findings from this review

suggest that ARBs are more effective than placebo therapy in long-term BP lowering in patients with essential hypertension. Long-term ARB treatment may also confer enhanced protection against stroke but no other cardiovascular outcomes relative to placebo.[7]

Effect of aliskiren on cardiovascular outcomes

The aim of this meta-analysis was to evaluate the effects of aliskiren monotherapy on major cardiovascular outcomes.[8] All eligible studies were RCTs assessing the effect of aliskiren therapy compared with patients not taking aliskiren therapy. Six trials reporting data on 12,465 patients were included in the review. Follow-up periods ranged from 8 weeks to 32 months. The trials were rated as moderate to high quality evidence. The studies reported 1,886 occurrences of major cardiovascular events, 1,074 events of total mortality, 739 events of cardiac death, 366 events of myocardial infarction, and 319 events of stroke.[8] Aliskiren therapy had no effect on major CV events (RR, 0.93; 95% CI: 0.77 to 1.13; P=0.47), total mortality (RR, 1.00; 95% CI: 0.77 to 1.29; P=1.00), cardiac death (RR, 1.01; 95% CI: 0.79 to .29; P=0.95), MI (RR, 0.71; 95% CI: 0.36 to 1.38; P=0.31), or stroke (RR, 0.87; 95% CI: 0.48 to 1.58; P=0.64).[8] The authors concluded aliskiren monotherapy does not have an effect on the incidence of major cardiovascular events, total mortality, cardiac death, myocardial infarction, or stroke.

New Guidelines:

Department of Veterans Affairs (VA), Department of Defense (DoD)

In 2014, the VA/DoD updated clinical practice guidelines focused on the management of hypertension originally published in 2004.[1] Recommended first line antihypertensive therapy for the general population including patients with coronary disease, MI or diabetes are thiazide diuretics. Second line therapy for the general patient population includes ACEIs, ARBs, or long acting dihydropyridine CCBs (amlodipine, felodipine or nifedipine SR). Additional drug classes may be added to reach blood pressure goals. Strong evidence recommends to avoid using ACEI, ARBs, and DRIs in combination with each other.

Recommendations for specific patient populations are as follows:

1. For patients with chronic kidney disease (CKD) ACEIs or ARBs are recommended as first line therapy.
2. ACEIs or ARBs are not recommended as monotherapy for African Americans.
3. For African Americans with CKD, combination therapy with thiazide diuretic and ACEI or ARB is recommended.

American Heart Association (AHA)/American College of Cardiology (ACC)/American Society of Hypertension (ASH)

Members of AHA, ACC and ASH collaborated to develop a scientific statement of treatment of hypertension in patients with coronary artery disease. This 2015 publication updated a 2007 AHA statement on treatment of hypertension in ischemic heart disease.[4] A summary of the main recommendations for pharmacologic treatment of hypertension in patients with ischemic heart disease is presented in **Table 1.**

Table 1. Pharmacologic Recommendations for treatment of hypertension in ischemic heart disease[4]

	ACEI or ARB	Diuretic	B-Blocker	Non-DHP CCB	DHP CCB	Nitrates	Aldosterone Antagonist	Hydralazine/Isosorbide
Stable Angina	Drug of Choice	Drug of Choice*	Drug of Choice	Add on or alternative drug – *do not use if HF or LVD is present. Caution should be exercised if combining non-DHP CCB with BB*	Add on or alternative drug	Drug of Choice	Add on or alternative drug	
ACS	Drug of Choice – *especially if prior MI, LVD,*	Drug of Choice*	Drug of Choice – *esmolol (IV), metoprolol or bisoprolol*	Add on or alternative drug- *do not use if HF or LVD is present. Caution should be exercised if combining non-DHP CCB with BB*	Add on or alternative drug	Add on or alternative drug	Add on or alternative drug –	

	DM or CKD is present						*spironolactone or epelrenone if LVD, HF, or DM is present*	
HF	Drug of Choice	Drug of Choice*	Drug of Choice – *carvedilol, metoprolol succinate, or bisoprolol*			Add on or alternative drug	Add on or alternative drug- *spironolactone or epelrenone if LVD, HF, or DM is present*	Add on or alternative drug

Abbreviations: ACS = acute coronary syndrome, BB = beta blocker, CCB = calcium channel blocker, CKD = chronic kidney disease, DHP = dihydropyridine, DM = Diabetes Mellitus, HF = heart failure, LVD = Left ventricular dysfunction, MI = myocardial infarction

** Chlorthalidone is preferred. Loop diuretic should be used in the presence of HF (New York Heart Association class III or IV) or CKD with glomerular filtration rate <30 mL/.min. Caution should be exercised in HF with preserved ejection fraction.*

National Institute for Health and Care Excellence (NICE) Guidance

NICE guidance regarding the utilization of sacubitril/valsartan for treating symptomatic chronic heart failure with reduced ejection fraction was published in 2016.[2] The recommendation is that sacubitril/valsartan is an option for patients with the following characteristics:

- with New York Heart Association (NYHA) class II to IV HF symptoms and
- with a left ventricular ejection fraction of 35% or less and
- who are already taking a stable dose of ACEI or ARB

This recommendation was primarily based on evidence from the PARADIGM-HF trial which compared sacubitril/valsartan 200 mg twice daily with enalapril 10 mg twice daily.[13] The primary end point from this trial was a composite of death from cardiovascular causes or a first hospitalization for worsening heart failure, assessed at every study visit (0, 2, 4 and 8 weeks, 4 months, and then every 4 months).[13] The composite primary end point significantly favored sacubitril/valsartan compared with enalapril (hazard ratio [HR] 0.80; 95% CI 0.73 to 0.87, p<0.001).[13] During the 27 month duration of this trial, the overall safety of sacubitril/valsartan was comparable to enalapril; although the sacubitril/valsartan cohort experienced more hypotension and the enalapril patients experienced more cough, the differences were not significant.[13] The NICE reviewers noted that PARADIGM-HF subjects were relatively younger, had a higher proportion of men, were less likely to be using cardiac devices, and had a higher tolerability to the dose of valsartan used in the trial (equivalent to 160 mg) which made the generalizability of the trial to the UK population more difficult. There are no head to head trials comparing sacubitril/valsartan with ARBs and long term safety data is lacking. More evidence evaluating the long term safety and comparative efficacy of sacubitril/valsartan will assist in identifying the role of this drug in HF management.

American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA): Update on New Pharmacological Therapy for Heart Failure

The 2016 ACC/AHA/HFSA publication focused on updating the 2013 ACCF/AHA guideline for the management of heart failure with sacubitril/valsartan and ivabradine.[3] In this document, sacubitril/valsartan is referred to as angiotensin receptor-neprilysin inhibitor (ANRI). Recommendations were classified according to estimated magnitude and certainty of benefit in the following categories: Class 1 (strong); Class IIa (moderate); Class IIb (weak); Class III: No Benefit; or Class III: Harm. Level of evidence was graded by the panel after reviewing the quality of data from clinical trials and meta-analyses. Level A evidence was categorized as high quality from RCTs or meta-analyses, level B-R was based on moderate quality evidence from RCT's or meta-analyses, level B-NR was moderate quality evidence from nonrandomized or observational data, level C-LD was based on data with methodological limitations, and Level C-EO was a consensus of expert

opinion based on clinical experience. The committee arrived at the recommendations for pharmacologic treatment of heart failure with reduced ejection fraction (HF*r*EF) as presented in **Table 2**.

Table 2. Treatment of Heart Failure: Recommendations for Renin-Angiotensin System Inhibition with ACE-I, ARB, or ARNI[3]

Recommendation	Class of Recommendation	Quality of Evidence
The clinical strategy of inhibition of the renin-aldosterone system with ACE inhibitors or ARBs or ARNI in conjunction with evidence based beta blockers and aldosterone antagonists in selected patients is recommended for patients with HF*r*EF.	Class I – Strong Benefit >>> Risk	ACE-I : A (High) ARB : A (High) ANRI: B-R (Moderate)
The use of ACE inhibitors is beneficial for patients with prior or current symptoms of chronic HF*r*EF to reduce morbidity and mortality.	Class I – Strong Benefit >>> Risk	A (High)
The use of ARBs to reduce morbidity and mortality is recommended in patients with prior or current symptoms of chronic HF*r*EF who are intolerant to ACE inhibitors because of cough or angioedema.	Class I –Strong Benefit >>> Risk	A (High)
In patients with chronic symptomatic HF*r*EF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality.	Class I- Strong Benefit >>> Risk	B-R (Moderate)
ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor.	Class III- Harm Risk > Benefit	B-R (Moderate)
ARNI should not be administered to patients with a history of angioedema.	Class III- Harm Risk > Benefit	C-EO (Expert Opinion)

New Formulations:

Qbrelis™

A new formulation of lisinopril, Qbrelis™ is a 1mg/ml oral solution FDA approved July 2016 for:

- treatment of hypertension in adults and pediatric patients ≥ 6 years
- adjunct therapy for heart failure
- treatment of acute myocardial infarction

This new oral liquid formulation of lisinopril provides more options for pediatric patients who require weight based dosing or older patients who have difficulty swallowing tablets. The FDA approval was based on two bioequivalence studies which were single dose crossover studies of lisinopril 10mg in fasting and fed states.[14] The application relied upon previously submitted safety and efficacy date for Zestril® (lisinopril) tablets.[14] Pediatric dosing of lisinopril was based on a 2003 dose- response RCT.[15]

Byvalson™

Byvalson™ is a new fixed dose combination therapy of a beta blocker and an ARB containing nebivolol 5 mg with valsartan 80 mg. It was FDA approved June 2016 for treatment of hypertension.[11] This is the first product to combine a beta blocker with an ARB and the only combination antihypertensive that contains

nebivolol. FDA approval was based on evidence supporting the utilization of combination therapy at lower doses to reduce dose-related adverse effects and provide additive treatment effects on blood pressure reduction.[16] Clinical trial data supporting the efficacy of the combination therapy was based on an 8 -week randomized, double -blind, placebo-controlled, parallel -group, multiple -dose study of nebivolol and valsartan given either as a fixed dose combination or as monotherapy in patients with Stage 1 or Stage 2 hypertension.[17] The trial included 4161 patients who were randomly assigned to receive double-blind treatment with nebivolol (5 mg/day or 20 mg/day) or valsartan (80 mg/day or 160 mg/day) monotherapies, fixed-dose combinations (FDC) of nebivolol and valsartan (5 and 80 mg/day, 5 and 160 mg/day, or 10 and 160 mg/day), or placebo. Nebivolol 5 mg in a fixed dose combination with valsartan 80 mg produced statistically and clinically significantly greater reductions in SBP/DBP at week 4 compared to the individual agents (least square mean (LSM) difference of 2.7/3.7 mm Hg for FDC 5/80mg vs nebivolol 5mg and LSM difference of 3.3/2.9 mm Hg FDC 5/80 mg vs valsartan 80mg).[17] The rate of treatment-emergent adverse effects was similar across all study groups. There is no current evidence that evaluates the long term safety and efficacy of this fixed dose combination of beta blocker and ARB therapy.

New Safety Alerts:

Olmesartan-associated sprue-like enteropathy

An association between olmesartan and severe sprue-like enteropathy was first described as a case series in 2012.[18] The clinical presentation was chronic diarrhea and median weight loss of 18 kg (range 2.5-57 kg) which required hospitalization in 14 out of 22 patients included in the initial report.[18] Duodenal biopsies of these patients revealed villous atrophy and inflammation. Withdrawal of olmesartan led to clinical and histological improvement.

An observational cohort study published in 2016 assessed the risk of hospitalization for intestinal malabsorption associated with olmesartan compared to other ACEIs and ARBs using the French National Insurance claim database.[19] Approximately 4,500,000 patients were included in the analysis and 218 events were observed. Eighty seven patients in the ACEI group, 48 patients in the olmesartan group, and 83 in the other ARB group were identified. Compared with ACEIs, the adjusted rate ratio of hospitalization with a discharge diagnosis of intestinal malabsorption was 2.49 (95% CI 1.73 to 3.57, $p<0.0001$) in olmesartan users.[19] Median length of hospital stay for intestinal malabsorption was longer in the olmesartan group than in the other ARB group (9 days vs 2 days; $p=0.02$).[19] The risks of intestinal disease increased with duration of exposure up to 10-fold beyond 2 years of exposure.[19] This data lead to the conclusion that olmesartan is associated with an increased risk of hospitalization for intestinal malabsorption. This risk has not been associated with treatment with other ARBs. The FDA issued a warnings and precautions update regarding the possibility of sprue-like enteropathy associated with olmesartan use in July, 2103.[12] If a patient develops these symptoms during treatment with olmesartan, providers are encouraged to exclude other etiologies and consider discontinuation of olmesartan in cases where no other etiology is identified.

ACE/ARB/DRI Utilization in Fee for Service Population

During the fourth quarter of 2016 (10/1/16 through 12/31/16) most claims for a preferred ACEI were for lisinopril (73%). The preferred ARB with the highest utilization was losartan with 21% of claims overall. Sixty four claims were received for nonpreferred agents in this class of antihypertensives. For the nonpreferred agents 71% (n=25) of claims were processed through the member's CCO insurance and most of the requests were for irbesartan. The remaining unfilled claims were due to loss of eligibility (n=5), coverage through Indian Health Service (n=1) or because a prior authorization was never requested (n = 4). Most of the FFS clients were able to receive ACEI or ARB therapy when it was prescribed by their provider. There was one paid claim for sacubitril/valsartan in all 4 quarters of 2016. There was one request for the direct renin inhibitor, aliskiren, but it was switched to another drug in the ACEI/ARB class.

References:

1. VA/DoD clinical practice guideline for the diagnosis and management of hypertension in the primary care setting. | National Guideline Clearinghouse. https://www.guideline.gov/summaries/summary/48858/vadod-clinical-practice-guideline-for-the-diagnosis-and-management-of-hypertension-in-the-primary-care-setting?q=treatment+of+hypertension. Accessed March 9, 2017.

2. Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction | 1-Recommendations | Guidance and guidelines | NICE. https://www.nice.org.uk/guidance/TA388/chapter/1-Recommendations. Accessed March 9, 2017.

3. Writing committee members, ACC/AHA task force members. 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Card Fail*. 2016;22(9):659-669. doi:10.1016/j.cardfail.2016.07.001.

4. Rosendorff C, Lackland DT, Allison M, et al. Treatment of hypertension in patients with coronary artery disease: A scientific statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension. *J Am Soc Hypertens*. 2015;9(6):453-498. doi:10.1016/j.jash.2015.03.002.

5. Li EC, Heran BS, Wright JM. Angiotensin converting enzyme (ACE) inhibitors versus angiotensin receptor blockers for primary hypertension. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 2014. doi:10.1002/14651858.CD009096.pub2.

6. Xue H, Lu Z, Tang WL, et al. First-line drugs inhibiting the renin angiotensin system versus other first-line antihypertensive drug classes for hypertension. *Cochrane Database Syst Rev*. 2015;1:CD008170. doi:10.1002/14651858.CD008170.pub2.

7. Akioyamen L, Levine M, Sherifali D, et al. Cardiovascular and cerebrovascular outcomes of long-term angiotensin receptor blockade: meta-analyses of trials in essential hypertension. *Journal of the American Society of Hypertension*. 2016;10(1):55-69. doi:10.1016/j.jash.2015.11.005.

8. Zhang J-T, Chen K-P, Guan T, Zhang S. Effect of aliskiren on cardiovascular outcomes in patients with prehypertension: a meta-analysis of randomized controlled trials. [Review]. *Drug design, development & therapy*. 2015:1963-1971. doi:10.2147/DDDT.S75111.

9. McMurray JJV, Krum H, Abraham WT, et al. Aliskiren, Enalapril, or Aliskiren and Enalapril in Heart Failure. *Journal of Medicine*. 2016;374(16):1521-1532. doi:10.1056/NEJMoa1514859.

10. CDER Application review of Byvlason™. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206302Orig1s000SumR.pdf. Accessed March 13, 2017.

11. Byvalson (valsartan/nebivolol) Prescribing Information. Irvine, CA. Allergan USA, Inc. June, 2016. https://www.allergan.com/assets/pdf/byvalson_pi. Accessed March 30, 2017.

12. Safety Information > Benicar (olmesartan medoxomil) Tablets. https://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm258781.htm. Accessed March 14, 2017.

13. McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993-1004. doi:10.1056/NEJMoa1409077.

14. CDER Evalution of Qbrelis™. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208401Orig1s000SumR.pdf. Accessed March 13, 2017.

15. Soffer B, Zhang Z, Miller K, Vogt BA, Shahinfar S. A double-blind, placebo-controlled, dose-response study of the effectiveness and safety of lisinopril for children with hypertension. *Am J Hypertens*. 2003;16(10):795-800.

16. Feldman RD, Zou GY, Vandervoort MK, Wong CJ, Nelson SAE, Feagan BG. A simplified approach to the treatment of uncomplicated hypertension: a cluster randomized, controlled trial. *Hypertension*. 2009;53(4):646-653. doi:10.1161/HYPERTENSIONAHA.108.123455.

17. Giles TD, Weber MA, Basile J, et al. Efficacy and safety of nebivolol and valsartan as fixed-dose combination in hypertension: a randomised, multicentre study. *Lancet*. 2014;383(9932):1889-1898. doi:10.1016/S0140-6736(14)60614-0.

18. Rubio-Tapia A, Herman ML, Ludvigsson JF, et al. Severe spruelike enteropathy associated with olmesartan. *Mayo Clin Proc*. 2012;87(8):732-738. doi:10.1016/j.mayocp.2012.06.003.

19. Basson M, Mezzarobba M, Weill A, et al. Severe intestinal malabsorption associated with olmesartan: a French nationwide observational cohort study. *Gut*. 2016;65(10):1664-1669. doi:10.1136/gutjnl-2015-309690.

Appendix 1: Current Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	CAPSULE	ALTACE	RAMIPRIL	Y
ORAL	CAPSULE	RAMIPRIL	RAMIPRIL	Y
ORAL	TABLET	BENAZEPRIL HCL	BENAZEPRIL HCL	Y
ORAL	TABLET	BENICAR	OLMESARTAN MEDOXOMIL	Y
ORAL	TABLET	COZAAR	LOSARTAN POTASSIUM	Y
ORAL	TABLET	ENALAPRIL MALEATE	ENALAPRIL MALEATE	Y
ORAL	TABLET	LISINOPRIL	LISINOPRIL	Y
ORAL	TABLET	LOSARTAN POTASSIUM	LOSARTAN POTASSIUM	Y
ORAL	TABLET	LOTENSIN	BENAZEPRIL HCL	Y
ORAL	TABLET	MICARDIS	TELMISARTAN	Y
ORAL	TABLET	PRINIVIL	LISINOPRIL	Y
ORAL	TABLET	TELMISARTAN	TELMISARTAN	Y
ORAL	TABLET	VASOTEC	ENALAPRIL MALEATE	Y
ORAL	TABLET	ZESTRIL	LISINOPRIL	Y
ORAL	SOLN RECON	EPANED	ENALAPRIL MALEATE	N
ORAL	SOLUTION	QBRELIS	LISINOPRIL	N
ORAL	TABLET	ACCUPRIL	QUINAPRIL HCL	N
ORAL	TABLET	ATACAND	CANDESARTAN CILEXETIL	N
ORAL	TABLET	AVAPRO	IRBESARTAN	N
ORAL	TABLET	CANDESARTAN CILEXETIL	CANDESARTAN CILEXETIL	N
ORAL	TABLET	CAPTOPRIL	CAPTOPRIL	N
ORAL	TABLET	DIOVAN	VALSARTAN	N
ORAL	TABLET	EDARBI	AZILSARTAN MEDOXOMIL	N
ORAL	TABLET	EPROSARTAN MESYLATE	EPROSARTAN MESYLATE	N
ORAL	TABLET	FOSINOPRIL SODIUM	FOSINOPRIL SODIUM	N
ORAL	TABLET	IRBESARTAN	IRBESARTAN	N
ORAL	TABLET	MAVIK	TRANDOLAPRIL	N
ORAL	TABLET	MOEXIPRIL HCL	MOEXIPRIL HCL	N
ORAL	TABLET	PERINDOPRIL ERBUMINE	PERINDOPRIL ERBUMINE	N
ORAL	TABLET	QUINAPRIL HCL	QUINAPRIL HCL	N
ORAL	TABLET	TEKTURNA	ALISKIREN HEMIFUMARATE	N
ORAL	TABLET	TRANDOLAPRIL	TRANDOLAPRIL	N
ORAL	TABLET	VALSARTAN	VALSARTAN	N
ORAL	TABLET	ENTRESTO	SACUBITRIL/VALSARTAN	

Current Status of PDL Class:

Preferred Drugs	Non-Preferred Drugs
Angiotensin Converting Enzyme Inhibitors	
Benazepril (*Lotensin*) Benazepril (*generic)* Enalapril (*Vasotec*) Enalapril *(generic)* Lisinopril (*Prinivil*; *Zestril*) Lisinopril *(generic*) Ramipril (*Altace*) Ramipril *(generic)*	Captopril (*generic*) Enalapril oral susp (*Epaned*) Lisinopril oral susp *(Qbrelis)* Fosinopril (*generic*) Moexipril (*Univasc*) Moexipril *(generic)* Perindopril (*Aceon*) Perindopril *(generic)* Quinapril (*Accupril*) Quinapril *(generic*) Trandolapril (*Mavik*) Trandolapril *(generic)*
Angiotensin II Receptor Antagonists	
Losartan (*Cozaar*) Losartan (*generic)* Olmesartan (*Benicar*) Olmesartan *(generic*) Telmisartan (*Micardis*) Telmisartan (*generic)*	Azilsartan (*Edarbi*) Candesartan (*Atacand*) Candesartan *(generic)* Eprosartan (*Teveten*) Eprosartan *(generic*) Irbesartan (*Avapro*) Irbesartan (*generic)* Valsartan (*Diovan*) Valsartan *(generic)*
Direct Renin Inhibitors	
	Aliskiren (*Tekturna*)
Other Cardiovascular Combination	
	Sacubitril/Valsartan *(Entresto)*

Appendix 2: New Comparative Clinical Trials

A total of 327 citations were manually reviewed from the initial literature search. After further review, 326 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 1 trial is summarized in the table below. Full abstract is included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

<table>
<tr><th>Study</th><th>Comparison</th><th>Population</th><th>Primary Outcome</th><th>Results</th></tr>
<tr>
<td>McMurray JV, etal[9]

DB, RCT, DD, MC</td>
<td>Enalapril 5 mg BID (low dose)
OR 10mg mg BID (high dose)
N = 2336

Vs

Aliskiren 300mg once daily
N = 2340

Vs

Aliskiren + Enalapril
N = 2340</td>
<td>HF with reduced ejection fraction defined as NYHA Class II to IV and EF ≤ 35% with BNP ≥ 150 pg/ml

Total N = 8835 patients</td>
<td>Primary composite outcome: death from CV causes or hospitalization for heart failure</td>
<td>
Table 1. Comparison of treatments for primary composite outcome: death from CV causes or first hospitalization for worsening HF
<table>
<tr><th>Treatment</th><th>Outcome (n)</th><th>Percent</th><th>Hazard Ratio for Primary Composite (95% CI)</th></tr>
<tr><td>Combination Therapy (Enalapril + Aliskiren)</td><td>Primary Composite (770)
Death from CV (512)
Hospitalization for HF (430)</td><td>32.9
21.9
18.4</td><td>Combo vs enalapril
0.93 (0.85 to 1.03) p = 0.17*</td></tr>
<tr><td>Enalapril</td><td>Primary Composite (808)
Death from CV (547)
Hospitalization for HF (452)</td><td>34.6
23.4
19.3</td><td></td></tr>
<tr><td>Aliskiren</td><td>Primary Composite (791)
Death from CV (562)
Hospitalization for HF (442)</td><td>33.8
24.0
18.9</td><td>Aliskiren vs enalapril
0.99 (0.9 to 1.1) p = 0.91*</td></tr>
<tr><td colspan="4">*Prespecified test for inferiority was not met</td></tr>
</table>
</td>
</tr>
</table>

Abbreviations: BNP B-type natriuretic peptide = BNP, CI = confidence interval, CV = cardiovascular, DB = double blind, DD = double dummy, EF = ejection fraction, HF = heart failure, MC = multi center, NYHA = New York Heart Association, RCT = randomized clinical trial

Appendix 3: Abstract of Comparative Clinical Trials

Aliskiren, Enalapril, or Aliskiren and Enalapril in Heart Failure[13]

John J.V. McMurray, M.D., Henry Krum, M.B., B.S., Ph.D., William T. Abraham, M.D., Kenneth Dickstein, M.D., Ph.D., Lars V. Køber, M.D., D.M.Sc., Akshay S. Desai, M.D., M.P.H., Scott D. Solomon, M.D., Nicola Greenlaw, M.Sc., M. Atif Ali, B.A., Yanntong Chiang, Ph.D., Qing Shao, Ph.D., Georgia Tarnesby, M.B., B.Chir., and Barry M. Massie, M.D., for the ATMOSPHERE Committees Investigators[†]

N Engl J Med 2016; 374(16): 1521-1532

Background

Among patients with chronic heart failure, angiotensin-converting–enzyme (ACE) inhibitors reduce mortality and hospitalization, but the role of a renin inhibitor in such patients is unknown. We compared the ACE inhibitor enalapril with the renin inhibitor aliskiren (to test superiority or at least noninferiority) and with the combination of the two treatments (to test superiority) in patients with heart failure and a reduced ejection fraction.

Methods

After a single-blind run-in period, we assigned patients, in a double-blind fashion, to one of three groups: 2336 patients were assigned to receive enalapril at a dose of 5 or 10 mg twice daily, 2340 to receive aliskiren at a dose of 300 mg once daily, and 2340 to receive both treatments (combination therapy). The primary composite outcome was death from cardiovascular causes or hospitalization for heart failure.

Results

After a median follow-up of 36.6 months, the primary outcome occurred in 770 patients (32.9%) in the combination-therapy group and in 808 (34.6%) in the enalapril group (hazard ratio, 0.93; 95% confidence interval [CI], 0.85 to 1.03). The primary outcome occurred in 791 patients (33.8%) in the aliskiren group (hazard ratio vs. enalapril, 0.99; 95% CI, 0.90 to 1.10); the prespecified test for noninferiority was not met. There was a higher risk of hypotensive symptoms in the combination-therapy group than in the enalapril group (13.8% vs. 11.0%, P=0.005), as well as higher risks of an elevated serum creatinine level (4.1% vs. 2.7%, P=0.009) and an elevated potassium level (17.1% vs. 12.5%, P<0.001).

Conclusions

In patients with chronic heart failure, the addition of aliskiren to enalapril led to more adverse events without an increase in benefit. Noninferiority was not shown for aliskiren as compared with enalapril.

Appendix 4: Medline Search Strategy

[Example]

Ovid MEDLINE(R) without Revisions 1996 to February Week 4 2017

1. *Angiotensin-Converting Enzyme Inhibitors/* *23015*
2. *Angiotensin Receptor Antagonists/ or Angiotensin II Type 1 Receptor Blockers/* *13666*
3. *ramipril.mp. or Ramipril/* *1942*
4. *benazepril.mp.* *556*
5. *Olmesartan Medoxomil/ or olmesartan.mp.* *1208*
6. *Losartan/* *5379*
7. *Enalapril/* *2969*
8. *Lisinopril/* *1344*
9. *telmisartan.mp.* *1761*
10. *quniapril.mp.* *1*
11. *candesartan.mp.* *2634*
12. *Captopril/* *3254*
13. *Valsartan/* *1913*
14. *azilsartan.mp.* *109*
15. *eposartan.mp.* *1*
16. *Fosinopril/* *310*
17. *irbesartan.mp.* *1484*
18. *trandolapril.mp.* *560*
19. *moexipril.mp.* *75*
20. *Perindopril/* *1244*
21. *quinapril.mp.* *541*
22. *aliskiren.mp.* *990*
23. *sacubitril.mp. or Valsartan/* *1947*
24. *1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 8 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or "24".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]* *21907*
25. *limit 24 to (humans and yr="2015-current" and (clinical trial, all or clinical trial or comparative study or controlled clinical trial or guideline or meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews))* *327*

Sacubitril/Valsartan (Entresto™)

Goal(s):
- Restrict use of sacubitril/valsartan in populations and at doses in which the drug has demonstrated efficacy.
- Encourage use of beta-blockers with demonstrated evidence of mortality reduction in heart failure with reduced ejection fraction.

Length of Authorization:
- 60 days to 12 months

Requires PA:
- Sacubitril/valsartan (Entresto™)

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is this a request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to Renewal Criteria	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code.	
3. Does the patient have stable New York Heart Association Class II or III heart failure with reduced ejection fraction less than 40% (LVEF <40%)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Has the patient tolerated a minimum daily dose an ACE-inhibitor or ARB listed in Table 1 for at least 30 days?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
5. Is the patient currently on a maximally tolerated dose of carvedilol, sustained-release metoprolol succinate, or bisoprolol; and if not, is there a documented intolerance or contraindication to each of these beta-blockers? *Note: the above listed beta-blockers have evidence for mortality reduction in chronic heart failure at target doses and are recommended by national and international heart failure guidelines.[1, 2] Carvedilol and metoprolol succinate are preferred agents on the PDL.*	**Yes:** Approve for up to 60 days	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is the patient currently taking sacubitril/valsartan at the target dose of 97/103 mg 2-times daily?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh and go to #2
2. What is the clinical reason the drug has not been titrated to the target dose of 97/103 mg 2-times daily?	Document rationale and approve for up to 60 days. Prior authorization required every 60 days until target dose achieved.	

Table 1. Minimum Daily Doses of ACE-inhibitors or ARBs Required.[1, 2]

ACE-inhibitor		Angiotensin-2 Receptor Blocker (ARB)	
Captopril	50 mg TID	Candesartan	32 mg QDay
Enalapril	10 mg BID	Losartan	150 mg QDay
Lisinopril	20 mg QDay	Valsartan	160 mg BID
Ramipril	5 mg BID		
Trandolapril	4 mg QDay		

Abbreviations: BID = twice daily; QDay = once daily; mg = milligrams; TID = three times daily.

Notes:
- Patients must achieve a minimum daily dose of one of the drugs listed for at least 30 days in order to improve chances of tolerability to the target maintenance dose of sacubitril/valsartan 97/103 mg 2-times daily.[3]
- Valsartan formulated in the target maintenance dose of sacubitril valsartan 97/103 mg 2-times daily is bioequivalent to valsartan 160 mg 2-times daily.[4]

- ACE-inhibitors and ARBs listed have demonstrated efficacy in heart failure with or without myocardial infarction.[1,2]
- Target daily doses of other ACE-inhibitors and ARBs for heart failure have not been established.[1,2]
- It is advised that patients previously on an ACE-inhibitor have a 36-hour washout period before initiation of sacubitril/valsartan to reduce risk of angioedema.[3,4]

References:
1. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62(16):e147-239. doi: 10.1016/j.jacc.2013.05.019.
2. McMurray J, Adamopoulos S, Anker S, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. European Journal of Heart Failure. 2012;14:803-869. doi:10.1093/eurjhf/hfs105.
3. McMurray J, Packer M, Desai A, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Eng J Med*. 2014;371:993-1004. doi:10.1056/NEJMoa1409077.
4. ENTRESTO (sacubitril and valsartan) [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals, July 2015.

P&T / DUR Review: *05/17(DM); 09/15*
Implementation: *10/1/15*