Drug Monograph

Drug/Drug Class: **Entresto™ (sacubitril and valsartan) tablet / Heart Failure**

Prepared for: MO HealthNet
Prepared by: Xerox Heritage, LLC

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Entresto™ is available as a film coated tablet in 3 different strengths. It is available in 24/26 mg, 49/51 mg, and 97/103 mg strengths of sacubitril/valsartan respectively. Manufacturer: Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936
Summary of Findings:	Entresto™ demonstrated efficacy in the randomized, double-blind, active-controlled PARADIGM-HF trial that included 8442 patients with NYHA class II to IV HF with an EF of 40% or less. Sacubitril/valsartan significantly reduced the composite outcome of CV death or hospitalization due to HF by 20% compared with enalapril, due to a reduction in both CV death and hospitalization due to HF. Death from any cause was also reduced from 19.8% with enalapril to 17% with combination therapy.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☒ Clinical Edit ☐ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☒ Appropriate Indications ☐ Non-Preferred Agent

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction[3]

Heart failure is a common condition affecting about 5.1 million people in the United States. It is a condition in which the heart can't pump enough blood to meet the body's needs. Heart failure generally worsens over time as the heart's pumping action grows weaker. The leading causes of heart failure are diseases that damage the heart, such as heart attacks and high blood pressure.

Dosage Form(s) [1]

Entresto™ is available as a film coated tablet in 3 different strengths. It is available in 24/26 mg, 49/51 mg, and 97/103 mg strengths of sacubitril/valsartan respectively.

Manufacturer [1]

Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936

Indication(s) [1]

Entresto™ is indicated for the treatment of adults with NYHA class II to IV chronic HF and reduced ejection fraction (EF) to reduce the risk of cardiovascular (CV) death and hospitalization due to HF.

Clinical Efficacy [1,2] (mechanism of action/pharmacology, comparative efficacy)

Entresto™ contains a neprilysin inhibitor, sacubitril, and an angiotensin receptor blocker, valsartan. Entresto™ inhibits neprilysin (neutral endopeptidase; NEP) via LBQ657, the active metabolite of the prodrug sacubitril, and blocks the angiotensin II type-1 (AT_1) receptor via valsartan. The cardiovascular and renal effects of Entresto in heart failure patients are attributed to the increased levels of peptides that are degraded by neprilysin, such as natriuretic peptides, by LBQ657, and the simultaneous inhibition of the effects of angiotensin II by valsartan. Valsartan inhibits the effects of angiotensin II by selectively blocking the AT_1 receptor, and also inhibits angiotensin II-dependent aldosterone release.

Pharmacokinetics:

	Sacubitril	**Valsartan**
Volume of distribution	103 L	75 L
Metabolism	Via esterases to LBQ657 (active)	Minimal (20%)
Excretion	Urine, 52% to 68% (primarily LBQ657) Feces, 37% to 48% (primarily LBQ657)	Urine, 13% Feces, 86%
Half-life	1.4 hours (unchanged), 11.5	9.9 hours

	hours (LBQ657)	
Protein binding	94% to 97%	94% to 97%

PARADIGM-HF TRIAL

Entresto™ reduced the risk of the combined endpoint of death from CV causes or hospitalization for HF, as well as death from any cause, in patients with HF.

STUDY DESIGN	Randomized, double-blind, active-controlled clinical trial (n=8442).
INCLUSION CRITERIA	Patients with NYHA class II, III, or IV HF and an EF of 40% or less (later amended to 35% or less).
EXCLUSION CRITERIA	Symptomatic hypotension, hyperkalemia, renal impairment, or a history of angioedema.
TREATMENT REGIMEN	Patients were randomized to receive Entresto™ 200 mg orally daily or enalapril 10 mg orally twice daily, in addition to standard treatment.
RESULTS	Entresto™ significantly reduced the risk of the combined endpoint of death from CV causes or hospitalization for HF by 20% compared with enalapril monotherapy (event rate, 21.8% for combination vs 26.5% for enalapril). Death from any cause was also reduced with combination therapy compared with enalapril (17% vs 19.8%), and this was related to the significant decrease in CV deaths (13.3% for combination vs 16.5% for enalapril). Hospitalization for HF was reduced by 21% with the combination therapy. Median duration of follow-up was 27 months.
SAFETY	Symptomatic hypotension occurred more often in the combination group (14% vs 9.2%), while cough (11.3% vs 14.3%), serum creatinine elevations of 2.5 mg/dL or higher (3.3% vs 4.5%), and elevated serum potassium of 6 mmol/L or higher (4.3% vs 5.6%) were reported more commonly in the enalapril group. Fewer patients in the combination group stopped therapy due to an adverse event (10.7% vs 12.3%) or renal impairment (0.7% vs 1.4%) compared with the enalapril group..

Contraindications [(1)]

- Angioedema to prior ACE inhibitor or angiotensin II receptor blocker therapy
- Concomitant aliskiren use in patients with diabetes
- Concomitant use of ACE inhibitors; do not administer within 36 hours of each other
- Hypersensitivity to sacubitril, valsartan, or any component of the product

Warnings and Precautions [(1)]

- Fetal injury or death may occur, particularly with second or third trimester exposure; discontinue use if pregnancy is detected.
- Angioedema may occur, including laryngeal edema that may be fatal; increased risk in

black patients and those with a prior history of angioedema; discontinue use.
- Symptomatic hypotension has been reported; dose reductions or treatment interruption may be required.
- Volume or salt depletion may increase the risk of symptomatic hypotension; correct prior to use; dose reduction or interruption of therapy may be warranted.
- Avoid use with angiotensin II receptor blockers.
- Avoid use with aliskiren in patients with renal impairment.
- Hyperkalemia may occur; monitoring recommended, especially in at-risk patients (eg, diabetes, a high potassium diet, hypoaldosteronism, severe renal impairment); dose reduction or treatment interruption may be required.
- Use not recommended in patients with severe hepatic impairment.
- Dose adjustments recommended in patients with moderate hepatic impairment.
- Decreases in renal function may occur.
- Increased risk of oliguria, progressive azotemia, acute renal failure and/or death in patients whose renal function is dependent on the renin-angiotensin system (eg, severe congestive heart failure); monitoring recommended.
- Increased serum creatinine or BUN may occur in patients with unilateral or bilateral renal artery stenosis; monitoring recommended.
- Dose adjustments recommended in patients with severe renal impairment.

Adverse Effects [(1)]

Most Common, ≥ 5%	Entresto™ (n=4203)	Enalapril (n=4229)
Hypotension	18%	12%
Hyperkalemia	12%	14%
Cough	9%	13%
Dizziness	6%	5%
Renal failure	5%	5%

Drug Interactions [(1)]

- ACE inhibitors
- Aliskiren
- Angiotensin II receptor blockers
- Lithium
- NSAIDS, including COX-2 inhibitors
- Potassium-sparing diuretics: spironolactone, triamterene, amiloride
- Potassium supplements or salt substitutes containing potassium

Dosage and Administration [(1)]

Initially, Entresto™ 49 mg/51 mg orally twice daily; increase the dose after 2 to 4 weeks, if tolerated, to a target maintenance dosage of Entresto™ 97 mg/103 mg twice daily. A lower starting dose is recommended for patients not switching from an ACE inhibitor or angiotensin II

receptor blocker or those receiving low doses of these agents, and for patients with severe renal impairment or moderate hepatic impairment.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST*/ MONTH
Sacubitril/ Valsartan	Entresto	Novartis	24 mg/26 mg tablets	1 tablet twice daily	$375.00
			49 mg/51 mg tablets	1 tablet twice daily	$375.00
			97 mg/103 mg tablets	1 tablet twice daily	$375.00

* Wholesale Acquisition Cost

Conclusion

Entresto™ is an oral combination of a novel neprilysin inhibitor and an angiotensin II receptor blocker that is indicated in adults with NYHA Class II to IV chronic HF and reduced EF to reduce the risk of CV death and hospitalization for HF. Entresto™ is typically administered along with other therapies for HF, in place of an ACE inhibitor or other angiotensin receptor blocker. It received fast track designation and priority review by the US Food and Drug Administration. A significant all-cause mortality benefit was shown in comparison with enalapril in the randomized, double-blind PARADIGM-HF clinical trial (n=8442), as well as significant improvements in the composite outcome of CV death or hospitalization due to HF. Treatment with Entresto™ resulted in a higher incidence of symptomatic hypotension than enalapril, but lower rates of cough, serum creatinine elevations of 2.5 mg/dL or higher, and elevated serum potassium to 6 mmol/L or higher.

Recommendation

The Division recommends adding this drug as a clinical edit.

References

1. Product Information: Entresto™, sacubitril/valsartan tablets. Novartis Pharmaceuticals Corp, East Hanover, NJ, 07/2015.
2. 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.
3. FDA approves new drug to treat heart failure. Retrieved 11/9/15 from : http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm453845.htm

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