Entresto® (sacubitril and valsartan) Clinical Summary for Formulary Review
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Indications and Usage[1]

Adult Heart Failure: Entresto is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction (HFrEF). Entresto is usually administered in conjunction with other heart failure therapies, in place of an angiotensin-converting enzyme (ACE) inhibitor or other angiotensin II receptor blocker (ARB).

Pediatric Heart Failure: for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. Entresto reduces NT-proBNP and is expected to improve cardiovascular outcomes.

Mechanism of Action[1]

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 (AT1) 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.

Dosage and Administration[1]

Entresto is contraindicated with concomitant use of an ACE inhibitor. If switching from an ACE inhibitor to Entresto allow a washout period of 36 hours between administration of the two drugs. **Adult Heart Failure**: The recommended starting dose of Entresto is 49/51 mg twice-daily. Double the dose of Entresto after 2 to 4 weeks to the target maintenance dose of 97/103 mg twice daily, as tolerated by the patient. **Pediatric Heart Failure**: Refer to Table 1 for the recommended dose for pediatric patients aged one year and older. Take the recommended dose orally twice daily. Adjust pediatric patient doses every 2 weeks, as tolerated by the patient.

Table 1: Recommended Dose Titration

	Titration Step Dose (twice daily)		
	Starting	**Second**	**Final**
Pediatric Patients Less than 40 kg†	1.6 mg/kg	2.3 mg/kg	3.1 mg/kg
Pediatric Patients At least 40 kg, less than 50 kg	24/26 mg	49/51 mg	72/78 mg‡
Pediatric Patients At least 50 kg	49/51 mg	72/78 mg‡	97/103 mg

† Use of the Oral Suspension recommended in these patients. Recommended mg/kg doses are of the combined amount of both sacubitril and valsartan
‡ Doses of 72/78 mg can be achieved using three 24/26 mg tablets

Dose Adjustment for Patients Not Taking an ACE inhibitor or ARB or Previously Taking Low Doses of These Agents

Start Entresto at half the usually recommended starting dose. After initiation, increase the dose to follow the recommended dose escalation thereafter. **Note**: Initiate pediatric patients weighing 40 to 50 kg who meet this criterion at 0.8 mg/kg twice daily using the oral suspension[1]

Dose Adjustment for Severe Renal Impairment (eGFR < 30 mL/min/1.73 m^2)

In adults and pediatric patients with severe renal impairment, start Entresto at half the usually recommended starting dose. After initiation, increase the dose to follow the recommended dose escalation thereafter No starting dose adjustment is needed for mild or moderate renal impairment. **Note:** Initiate pediatric patients weighing 40 to 50 kg who meet this criterion at 0.8 mg/kg twice daily using the oral suspension[1].

Dose Adjustment for Hepatic Impairment

In adults and pediatric patients with moderate hepatic impairment (Child-Pugh B classification), start ENTRESTO at half the usually recommended starting dose. After initiation, increase the dose to follow the recommended dose escalation thereafter. No starting dose adjustment is needed for mild hepatic impairment. Use in patients with severe hepatic impairment is not recommended. **Note:** Initiate pediatric patients weighing 40 to 50 kg who meet this criterion at 0.8 mg/kg twice daily using the oral suspension[1]

Efficacy

Adult Heart Failure

PARADIGM-HF: The efficacy and safety of Entresto was evaluated in PARADIGM-HF, a multinational, randomized, double-blind (DB) trial comparing Entresto and enalapril in 8,442 adult patients with symptomatic chronic heart failure (NYHA class II–IV) and systolic dysfunction (left ventricular ejection fraction [LVEF] ≤ 40%).[1]

- Patients had to have been on an ACE inhibitor or ARB for at least four weeks and on maximally tolerated doses of beta-blockers. Patients with a systolic blood pressure (SBP) of <100 mmHg at screening were excluded.[1]
- The primary objective was to determine whether Entresto, a combination of sacubitril and a RAS inhibitor (valsartan), was superior to a RAS inhibitor (enalapril) alone in reducing the risk of the combined endpoint of cardiovascular (CV) death or hospitalization for heart failure (HF).[1]
- After discontinuing existing ACE inhibitor or ARB therapy, patients entered sequential single-blind run-in periods during which they received enalapril 10 mg twice-daily, followed by Entresto 49/51 mg twice daily, increasing to 97/103 mg twice daily. Patients who successfully completed the sequential run-in periods were randomized to receive either Entresto 97/103 mg (N=4,209) or enalapril 10 mg (N=4,233), given twice daily.
- The primary endpoint was the first event in the composite of CV death or hospitalization for HF. The median follow-up duration was 27 months and patients were treated for up to 4.3 years.[1]
- The population was 66% Caucasian, 18% Asian, and 5% Black; the mean age was 64 years and 78% were male. Most patients were taking beta-blockers (94%), mineralocorticoid antagonists (58%), and diuretics (82%).
- PARADIGM-HF demonstrated that Entresto was superior to enalapril in reducing the risk of the combined endpoint of CV death or hospitalization for HF, based on a time-to-event analysis (hazard ratio [HR]: 0.80, 95% confidence interval [CI], 0.73, 0.87, p <0.0001). The treatment effect reflected a reduction in both CV death and HF hospitalization. Sudden death accounted for 45% of CV deaths, followed by pump failure, which accounted for 26%. Entresto also improved overall survival (HR 0.84; 95% CI [0.76, 0.93], P=0.0009), .[1]
- In a post-hoc analysis of PARADIGM-HF, treatment with Entresto reduced the 30-day readmissions for HFrEF after a HFrEF hospitalization compared with enalapril (9.7% vs 13.4%; OR 0.62; 95% CI: 0.45, 0.87; P=0.006).[3]
- Entresto decreased plasma NT-proBNP and increased plasma BNP compared with enalapril.[1]

Entresto is recommended by the 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure for patients with chronic HFrEF in conjunction with beta-blockers and aldosterone antagonists in selected patients to reduce morbidity and mortality. In patients with chronic symptomatic HFrEF NYHA Class II or III who tolerate an ACEI or ARB, replacement by Entresto is recommended to further reduce morbidity and mortality.[2]

PIONEER-HF: The safety, tolerability and efficacy of in-hospital initiation of Entresto compared with enalapril in 881 patients with HFrEF after stabilization during a hospitalization for acute decompensated heart failure (ADHF) was evaluated in PIONEER-HF, a prospective, multicenter, DB, randomized, active-controlled, 8-week study.[4]

- Patients had to be hospitalized for ADHF (with signs and symptoms of fluid overload) and have a LVEF ≤40% within past 6 months. They were permitted to be on variable doses of ACE inhibitors or ARBs or were treatment naive (not receiving ACEI/ARB at the time of index hospitalization), and were stabilized. Stabilization was defined as: SBP ≥100 mmHg for at least 6 hours prior to randomization, with no symptomatic hypotension, no increase in intravenous (IV) diuretic dose or use of IV vasodilators including nitrates within the last 6 hours prior to randomization, and no IV inotropes for 24 hours prior to randomization.
- Patients were randomized 1:1 to Entresto or enalapril ≥24 hours and up to 10 days after initial presentation to the hospital, while still hospitalized. Patients randomized to enalapril received the active study drug at the first dose. Patients randomized to Entresto first received 2 doses of placebo to ensure a 36-hour washout period. All patients were monitored for 6 hours after the 3rd dose; after which investigators were allowed to discharge patients at any point based on their discretion.

- In the DB treatment period, Entresto was dosed using a dose titration algorithm based on SBP [8]:
  - Starting dose for SBP >100 and <120 mmHg was Entresto 24/26 mg or enalapril 2.5 mg twice daily, and for SBP ≥120 mmHg was Entresto 49/51 mg or enalapril 5 mg twice daily.
  - At Week 1, dose was titrated upwards if SBP >110 mmHg. At Weeks 2, 4, and 6, dose was titrated upwards if SBP >100 mmHg.
  - Dosage was titrated up to the target dose of Entresto 97/103 mg twice daily and enalapril 10 mg twice daily per protocol-defined safety and tolerability criteria and investigator judgment
- The primary endpoint was the time-averaged proportional change in NT-proBNP from baseline through Weeks 4 and 8.
- At Baseline, mean age was 61±14 years, 635 (72.1%) of patients were male, and 316 (35.9%) were Black. Additionally, 459 (52.1%) were ACEI/ARB naive (not receiving treatment with ACEI/ARB at time of index hospitalization), and 303 (34.4%) had de novo HFrEF. Median duration of index hospitalization was 5.20 days (interquartile range, 4.09 to 7.24). During the index hospitalization, but prior to randomization, 93% of patients received intravenous (IV) furosemide, 7.7% received IV inotropes, and 11% were in the intensive care unit. By Week 8, 243 (55.2%) and 268 (60.8%) of patients were receiving target dose of Entresto and enalapril, respectively.
- PIONEER-HF demonstrated that Entresto significantly reduced NT-proBNP levels from baseline to Weeks 4 and 8 compared with enalapril (ratio of change 0.71, 95% CI [0.63-0.81], P<0.001); effects were consistent across subgroups analyzed including ACEi/ARB naive and de novo HFrEF.
- After 8 weeks, rehospitalization for HF occurred in 35 patients (8.0%) in the Entresto group and 61 patients (13.8%) in the enalapril group (HR 0.56, 95% CI 0.37-0.84).[4]

***Pediatric Heart Failure*-PANORAMA-HF**:
The efficacy of Entresto was evaluated in a multinational, randomized, double-blind trial comparing Entresto and enalapril based on an analysis in 110 pediatric patients 1 to <18 years old with heart failure (NYHA/Ross class II-IV) due to systemic left ventricular systolic dysfunction (LVEF ≤40%). Patients with systemic right ventricles and single ventricles were excluded from the trial. The target maintenance dose of Entresto in pediatric patients 1 to <18 years old was 3.1 mg/kg twice daily. The endpoint was the between-group difference in the change in plasma NT-proBNP from baseline to 12 weeks. The reduction from baseline in NT-proBNP was 44% and 33% in the Entresto and enalapril groups, respectively. While the between-group difference was not statistically significant, the reductions for Entresto and enalapril were similar to or larger than what was seen in adults; these reductions did not appear to be attributable to post-baseline changes in background therapy. Because Entresto improved outcomes and reduced NT-proBNP in PARADIGM-HF, the effect on NT-proBNP was considered a reasonable basis to infer improved cardiovascular outcomes in pediatric patients.[1]

Adverse Event Profile
PARADIGM-HF: In the PARADIGM-HF trial, subjects were required to complete sequential enalapril and Entresto run-in periods of (median) 15 and 29 days, respectively, prior to entering the randomized DB period comparing Entresto and enalapril. During the enalapril run-in period, 1,102 patients (10.5%) were permanently discontinued from the study, 5.6% because of an adverse event (AE), most commonly renal dysfunction (1.7%), hyperkalemia (1.7%) and hypotension (1.4%). During the Entresto run-in period, an additional 10.4% of patients permanently discontinued treatment, 5.9% because of an AE, most commonly renal dysfunction (1.8%), hypotension (1.7%) and hyperkalemia (1.3%). Because of the run-in design, the adverse reaction rates reported during the DB period are lower than expected in practice. During the DB period the most common adverse reactions occurring at an incidence of ≥5% in patients who were treated with Entresto were hypotension (18%), hyperkalemia (12%), cough (9%), dizziness (6%), and renal failure/acute renal failure (5%).[1]
PIONEER-HF: There were no significant differences observed in incidence of key safety endpoints including incidence of worsening renal function (defined as an increase in serum creatinine (SCr) ≥0.5 mg/dL with a worsening of estimated glomerular filtration rate (eGFR) ≥25%); incidence of symptomatic hypotension; incidence of hyperkalemia (defined as serum potassium >5.5 mmol/L); incidence of angioedema. During the DB period the most common AEs occurring at an incidence of ≥5% in patients who were treated with Entresto were acute kidney injury (8.2%), blood creatinine increased (7.1%), cardiac failure congestive (5.0%), dizziness (8.9%), hyperkalemia (12.5%), and hypotension (18.0%).[4]
Pediatric Heart Failure: The adverse reactions observed in pediatric patients 1 to <18 years old who received treatment with Entresto were consistent with those observed in adult patients[1]

Contraindications[1]
Entresto is contraindicated:
- in patients with hypersensitivity to any component.
- in patients with a history of angioedema related to previous ACE inhibitor or ARB therapy.
- with concomitant use of ACE inhibitors. Do not administer within 36 hours of switching from or to an ACE inhibitor.
- with concomitant use of aliskiren in patients with diabetes.

Warnings and Precautions[1]
- *Fetal Toxicity*: Entresto can cause fetal harm when administered to a pregnant woman. When pregnancy is detected, consider alternative drug treatment and discontinue Entresto. However, if there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system, and if the drug is considered lifesaving for the mother, advise a pregnant woman of the potential risk to the fetus.
- *Angioedema*: Entresto may cause angioedema. In the double-blind period of PARADIGM-HF, 0.5% of patients treated with Entresto and 0.2% of patients treated with enalapril had angioedema. If angioedema occurs, discontinue Entresto immediately, provide appropriate therapy, and monitor for airway compromise. Entresto must not be re-administered. Entresto has been associated with a higher rate of angioedema in Black than in non-Black patients. Patients with a prior history of angioedema may be at increased risk of angioedema with Entresto. Entresto must not be used in patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy or in patients with hereditary angioedema.
- *Hypotension*: Entresto lowers blood pressure and may cause symptomatic hypotension. Patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients, are at greater risk. PARADIGM-HF, 18% of patients treated with Entresto and 12% of patients treated with enalapril reported hypotension as an adverse event, with hypotension reported as a serious adverse event in approximately 1.5% of patients in both treatment arms. Correct volume or salt depletion prior to administration of Entresto or start at a lower dose. If hypotension occurs, consider dose adjustment of diuretics, concomitant antihypertensive drugs, and treatment of other causes of hypotension. If hypotension persists despite such measures, reduce the dosage or temporarily discontinue Entresto. Permanent discontinuation of therapy is usually not required.
- *Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, decreases in renal function may be anticipated in susceptible individuals treated with Entresto. In the double-blind period of PARADIGM-HF, 5% of patients in both the Entresto and enalapril groups reported renal failure as an adverse event. In patients whose renal function depends upon the activity of the renin-angiotensin-aldosterone system treatment with ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria, progressive azotemia and, rarely, acute renal failure and death. Closely monitor serum creatinine, and down-titrate or interrupt Entresto in patients who develop a clinically significant decrease in renal function. As with all drugs that affect the RAAS, Entresto may increase blood urea and serum creatinine levels in patients with bilateral or unilateral renal artery stenosis. In patients with renal artery stenosis, monitor renal function.
- *Hyperkalemia:* Through its actions on the RAAS, hyperkalemia may occur with Entresto. In the double-blind period of PARADIGM-HF, 12% of patients treated with Entresto and 14% of patients treated with enalapril reported hyperkalemia as an adverse event. Monitor serum potassium periodically and treat appropriately, especially in patients with risk factors for hyperkalemia such as severe renal impairment, diabetes, hypoaldosteronism, or a high potassium diet. Dosage reduction or interruption of Entresto may be required.

Please see accompanying full Entresto Prescribing Information.

References

1. Entresto (sacubitril/valsartan) [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation. October 2019
2. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused 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. *Circulation*. 2017;136(6):e137-e161.
3. Desai AS, Claggett BL, Packer M, et al. Influence of sacubitril/valsartan (LCZ696) on 30-day readmission after heart failure hospitalization. *J Am Coll Cardiol*. 2016;68(3):241-248.
4. Velazquez EJ, Morrow DA, Devore AD, et al. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med.* 2018; Nov 11. doi. 10.1056/NEJMoa1812851