PDL DRUG REVIEW

Proprietary Name: Entresto®
Common Name: sacubitril/valsartan
PDL Category: ARB Combinations

Comparable Products	Preferred Drug List Status
Enalapril	Preferred

Summary

Pharmacology/Usage: Entresto® is a combination product that contains sacubitril (a neprilysin inhibitor) and valsartan (an angiotensin II receptor blocker or ARB). Entresto® inhibits neprilysin (neutral endopeptidase; NEP) via LBQ657, the active metabolite of the prodrug sacubitril; and, it blocks the angiotensin II type-1 (AT1) receptor via valsartan. *Per the prescribing information*: 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

Indication: 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. Entresto® is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.

There is no pregnancy category listed for this product; however, the risk summary indicates that Entresto® can cause fetal harm if administered to a pregnant woman. When pregnancy is detected, consider other alternative drug treatment and discontinue Entresto® treatment. However, if no appropriate alternative therapy is available and if the drug is considered life-saving to the mother, advise a pregnant women of the potential risk to the fetus. Entresto® does have a box warning of fetal toxicity and that it can cause fetal harm if administered to a pregnant woman. Use of drugs that act on the renin angiotensin system during the 2nd and 3rd trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. The safety and efficacy of use in children under the age of 18 years have not been established.

Dosage Forms: Film-coated Tablets: 24/26mg, 49/51mg, and 97/103mg

Recommended Dosage: The concomitant use of Entresto® with an ACE-Inhibitor is contraindicated; if switching from an ACE-Inhibitor to Entresto®, allow for a washout period of 36 hours between administration of the two drugs. Initiate treatment at 49/51mg BID and titrate after 2-4 weeks to the target maintenance dose of 97/103mg BID, as tolerated; however, for patients not currently taking an ACE inhibitor or an ARB and for patients previously taking low doses of these agents, start treatment at 24/26mg BID and titrate as above.

Dose adjustments are not required for those with mild hepatic or mild to moderate renal impairment; however, a starting dose of 24/26mg BID is recommended for patients with severe renal impairment (eGFR

<30ml/min/1.73m^2) and for patients with moderate hepatic impairment. Titrate as above. Use is not recommended in patients with severe hepatic impairment.

Drug Interactions: Concomitant use of Entresto® with an ACE inhibitor (due to increased risk of angioedema) or with aliskiren in patients with diabetes are contraindicated. In addition, the concomitant use of Entresto® with an ARB should be avoided. Concomitant use of Entresto® with potassium-sparing diuretics, potassium supplements, or salt substitutes may lead to increases in serum potassium. Serum lithium levels should be monitored during concomitant use with Entresto®. In patients who are elderly, volume-depleted, or with compromised renal function, concomitant use of NSAIDs with Entresto® may cause worsening of renal function. While these effects are generally reversible, renal function should be monitored periodically.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Entresto®) minus reported % incidence for enalapril. Please note that an incidence of 0% means the incidence was the same or that the active drug was less than its comparator.* The most frequently reported adverse events included hypotension (6%), hyperkalemia (0%), cough (0%), dizziness (1%), renal failure/acute renal failure (0%), angioedema (0.3%), orthostasis (1%), and falls (0.6%). Reported lab abnormalities included decreases in hemoglobin/hematocrit >20% (0%), increases in serum creatinine of >50% (0%), and potassium concentrations >5.5mEq/L (0%).

Contraindications: In patients with hypersensitivity to any component of the compound; In patients with a history of angioedema related to a 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.

Manufacturer: Novartis

Analysis: The safety and efficacy of Entresto® was assessed in the PARADIGM-HF study, a multicenter, randomized, double-blind study that compared Entresto® with enalapril in adults (N=8442) with symptomatic chronic heart failure (NYHA class II-IV) and systolic dysfunction. Patients had to have been on an ACE-I or an ARB for at least 4 weeks and on maximally tolerated doses of beta-blockers; those with systolic BP <100mmHg at screening were excluded. The primary outcome 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.

Results suggested that Entresto® was superior to enalapril for reducing the risk of the combined endpoint (hazard ratio [HR] 0.80; p<0.0001). Both a reduction in CV death and heart failure hospitalization was seen. Entresto® also improved overall survival (HR 0.84; p=0.0009). The table below, adapted from the prescribing information, illustrates the results.

	Entresto® (N=4187)	Enalapril (N=4212)	Hazard Ratio/p-value
Primary composite endpoint	21.8%	26.5%	0.80; p<0.0001
CV death as first event	9%	10.9%	
Heart failure hospitalization as first event	12.8%	15.6%	
Number of Patients w/CV death	13.3%	16.5%	
Number of patients w/heart failure hospitalizations	12.8%	15.6%	
All-cause mortality	17%	19.8%	0.84; p=0.0009

Place in Therapy: There is good quality data that suggests this drug is more effective than an ACE-I alone in reducing the rate of death from cardiovascular causes or hospitalization for heart failure. The data supports this use of this drug in those with NYHA Class II-IV heart failure and a reduced ejection fraction. It is recommended that Entresto® remain non-preferred and require prior authorization to ensure that is used in accordance with the approved indications.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☒ **Refer to DUR for PA Criteria**

References

[1] Entresto [package insert]. East Hanover, NJ: Novartis; 2015.

[2] UpToDate desktop version. Use of angiotensin II receptor blocker and neprilysin inhibitor in heart failure with reduced ejection fraction. Accessed September 2015.