Brand Name:

Entresto

Generic Name:

Sacubitril and valsartan.

Manufacturer[1]:

Novartis

Indication (FDA and off-labeled)[1]:

Labeled

Chronic Class II-IV Heart Failure

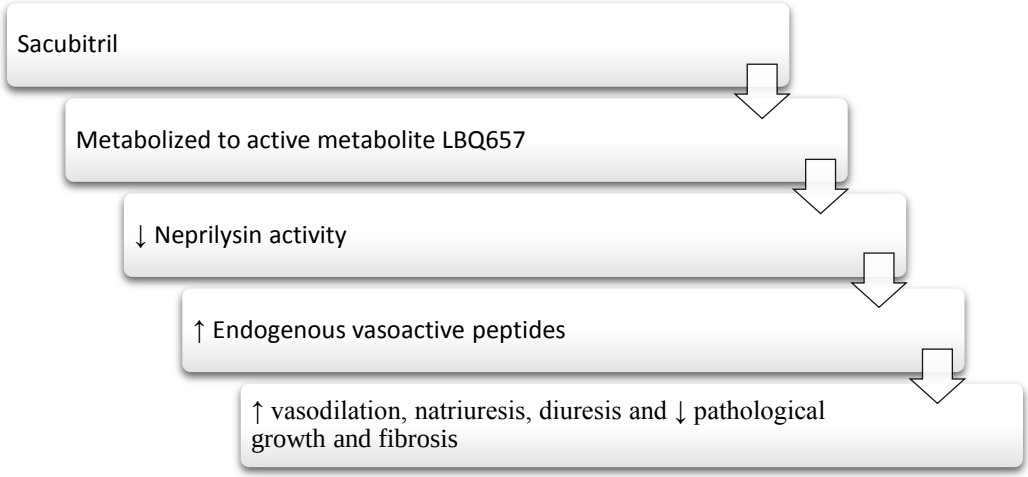
Off-labeled

No current off-label uses.

Mechanism of action[1,2,3,4]:

Sacubitril

Sacubitril is a prodrug metabolized to an active metabolite called LBQ657. LBQ657 inhibits neprilysin, which is responsible for degrading endogenous vasoactive peptides (i.e. natriuretic peptides, bradykinin, and adrenomedullin). As these peptide levels remain elevated in the body, their activities are prolonged, resulting in vasodilation, natriuresis, diuresis, and inhibition of pathologic growth and fibrosis.



Valsartan

Valsartan is an angiotensin receptor blocker that selectively blocks the AT1 receptors, inhibiting angiotensin-II dependent vasoconstriction, aldosterone release, catecholamine release, arginine vasopressin release, water intake, and hypertrophic responses.

Pharmacokinetics[1,2,3,4]:

	Sacubitril	LBQ657	Valsartan
Tmax	0.5 hours	2 hours	1.5 hours
Vd	103L	Not Reported	75L
t½	1.4 hours	11.5 hours	9.9 hours
Clearance	Not Reported	Not Reported	Not Reported
Protein Binding (albumin bound)	94%-97%	Bound as sacubitril	94%-97%
Bioavailability	>60%	Bioavailable as sacubitril	More bioavailable than other marketed formulations*

* 26mg, 51mg, and 103mg of valsartan in Entresto is equivalent to 40mg, 80mg, and 160mg in other marketed formulations of valsartan on the market.

Metabolism

Sacubitril

Readily metabolized to LBQ657 by esterases in the blood.

Valsartan

Minimally metabolized. 20% of dose is recovered as metabolites (<10% found as a hydroxyl metabolite).

Elimination

Sacubitril

Sacubitril is primarily eliminated through the kidneys. 52% to 68% is excreted in the urine, mostly as its metabolite LBQ657.

The remainder of the drug, 37% - 48%, is excreted in the feces.

Valsartan

86% of Valsartan is excreted in the feces. ~13% of valsartan and its metabolites are excreted in the urine.

Efficacy:

Solomon, Scott D., Michael Zile, and Burkert Pieske. "The Angiotensin Receptor Neprilysin Inhibitor LCZ696 in Heart Failure with Preserved Ejection Fraction: A Phase 2 Double-blind Randomised Controlled Trial." *The Lancet* 380.9851 (2012): 1387-395. Web. [5]

Study Design:

A phase 2, randomized, parallel-group, double-blind multicenter trial in patients with New York Heart Association (NYHA) class II–III heart failure and preserved ejection fraction.

Description:

This study assessed the efficacy and safety of LCZ696 using data from the phase II PARAMOUNT clinical trial for its evaluation. Participants were randomly assigned (1:1) by central interactive voice response system to LCZ696 titrated to 200 mg twice daily or valsartan titrated to 160 mg twice daily, and treated for 36 weeks. The primary endpoint was change in NT-proBNP, a marker of left ventricular wall stress, from baseline to 12 weeks. 149 patients were randomly assigned to LCZ696 and 152 to valsartan; 134 in the LCZ696 group and 132 in the valsartan group were included in analysis of the primary endpoint. NT-proBNP was significantly reduced at 12 weeks in the LCZ696 group compared with the valsartan group (LCZ696: baseline, 783 pg/mL [95% CI 670–914], 12 weeks, 605 pg/mL [512–714]; valsartan: baseline, 862 pg/mL [733–1012], 12 weeks, 835 [710–981]; ratio LCZ696/valsartan, 0·77, 95% CI 0·64–0·92, p=0·005). LCZ696 was well tolerated with adverse effects similar to those of valsartan; 22 patients (15%) on LCZ696 and 30 (20%) on valsartan had one or more serious adverse event. Serious adverse events were listed as death, cardiac, heart failure, acute coronary syndrome, and renal.

Limitations:

The funding was provided by Novartis, the manufacturer of Entresto, and several authors of this study are either employees of Novartis or have received funding by the company.

Conclusion:

In patients with heart failure and preserved ejection fraction, LCZ696 reduced NT-proBNP to a greater extent than did valsartan at 12 weeks, and was associated with left atrial reverse remodeling at 36 weeks and improvement in NYHA class at 36 weeks, consistent with the hypothesis that LCZ696 reduced left ventricular pressures and wall stress. These findings suggest that LCZ696 could have profound favorable effects in this patient population.

Voors, Adriaan A., Mauro Gori, and Licette C.y. Liu. "Renal Effects of the Angiotensin Receptor Neprilysin Inhibitor LCZ696 in Patients with Heart Failure and Preserved Ejection Fraction." ***Eur J Heart Fail European Journal of Heart Failure*** **17.5 (2015): 510-17. Web.[6]**

Study Design:

A phase 2, randomized, parallel-group, double-blind multicenter trial in patients with New York Heart Association (NYHA) class II–III heart failure and preserved ejection fraction.

Description:

This study used data gathered from the phase II PARAMOUNT clinical trial to determine the effects of LCZ696 on renal function. Renal function was evaluated in this article by serum creatinine, eGFR, cystatin C, urinary albumin to creatinine ratio (UACR) and worsening renal function. Furthermore, worsening renal function was determined as a serum creatinine increase of >0.3mg/dL and/or >25% between two time-points. Mean

eGFR at baseline was 65.4±20.4mL/min per 1.73m2. The eGFR declined less in the LCZ696 group than in the valsartan group (–1.5 vs. –5.2mL/min per 1.73m2; *P* =0.002). The incidence of renal deterioration was lower in the LCZ696 group (12%) than in the valsartan group (18%) at any time-point, but this difference was not statistically significant (*P* =0.18). Over 36 weeks, the geometric mean of the urine albumin-creatinine ratio increased in the LCZ696 group (2.4–2.9 mg/mmol), whereas it remained stable in the valsartan group (2.1–2.0 mg/mmol; *P* for difference between groups=0.016).

Limitations:

The funding was provided by Novartis, the manufacturer of Entresto, and several authors conducting the post hoc review of the PARAMOUNT trial are either employees of Novartis or have received funding by the company. Additionally the post hoc nature of the study itself is also considered a large limitation, as they were only able to evaluate previously reported data. With that, only patients with an estimated glomerular filtration rate of at least 30 mL/min.1.73 m^2 were included in the clinical trial, excluding any assessment of patients with severely impaired renal function. The renal variables of interest were not available for all patients for unknown reasons, and may thus have biased the results even though the numbers of missing were small. Lastly, the PARAMOUNT trial was not originally designed to evaluate the renal effects of LCZ696 and because of the low number of patients, this study may have been underpowered.

Conclusion:

In heart failure patients with preserved ejection fraction, LCZ696 better preserved renal function compared with valsartan after 36 weeks of therapy, as was shown by lower levels of serum creatinine and higher eGFR. These results suggest that LCZ696 may attenuate decline in renal function in heart failure patients with preserved ejection fraction.

McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993–1004.[7]

Study Design:

A phase III, multinational, randomized, double-blinded trial comparing Entresto and enalapril in 8,442 adult patients with symptomatic chronic heart failure (NYHA class II-IV) and reduced ejection fraction.

Description:

The primary objective of the trial was to determine whether Entresto was superior to enalapril alone in reducing the risk of cardiovascular death or hospitalization in heart failure. After discontinuing their existing ACE inhibitor or ARB therapy, patients entered a single-blind run-in period during which they received enalapril 10mg twice daily, followed by Entresto 100mg twice daily, increasing to 200mg twice daily. Patients who

successfully completed the run in periods were randomized to receive either Entresto 200mg twice daily or enalapril 10mg twice daily. The primary endpoint was the occurrence of cardiovascular death or hospitalization associated with heart failure. The median follow-up duration was 27 months and patients were treated for up to 4.3 years.

The trial was stopped early after a median follow-up of 27 months, because the boundary for an overwhelming benefit with Entresto had been crossed. At the time of study closure, the primary outcome had occurred in 914 patients (21.8%) in the Entresto group and 1117 patients (26.5%) in the enalapril group (hazard ratio in the Entresto group, 0.80; 95% confidence interval [CI], 0.73 to 0.87; P<0.001). A total of 711 patients (17.0%) receiving Entresto and 835 patients (19.8%) receiving enalapril died (hazard ratio for death from any cause, 0.84; 95% CI, 0.76 to 0.93; P<0.001); of these patients, 558 (13.3%) and 693 (16.5%), respectively, died from cardiovascular causes (hazard ratio, 0.80; 95% CI, 0.71 to 0.89; P<0.001). As compared with enalapril, Entresto also reduced the risk of hospitalization for heart failure by 21% (P<0.001) and decreased the symptoms and physical limitations of heart failure (P=0.001). The Entresto group had higher proportions of patients with hypotension and non-serious angioedema but lower proportions with renal impairment, hyperkalemia, and cough than the enalapril group.

Limitations:

Two major limitations existed in the study that are worth noting. This study was conducted and funded by Novartis and employees of Novartis. Secondly, the study compared the max dose of Entresto (200mg twice daily) to a sub-maximal dose of enalapril.

Conclusion:

The study demonstrated that Entresto was superior to enalapril in reducing the risk of cardiovascular death or hospitalization for heart failure patients, based on a time-to-event analysis (hazard ratio [HR]: 0.08, 95% confidence interval [CI], 0.73, 0.87, p<0.0001). The treatment effect reflected a reduction in both cardiovascular death and heart failure hospitalizations. Entresto also improved overall survival (HR 0.84; 95% CI [0.76, 0.93], p=0.0009). However, the limitations of the study should be taken into account before finding a place in current therapy recommendations.

Mcmurray, J., M. Packer, and A. Desai. "A Putative Placebo Analysis of the Effects of LCZ696 on Clinical Outcomes in Heart Failure." *European Heart Journal* 36.7 (2014): 434-39. Web.[8]

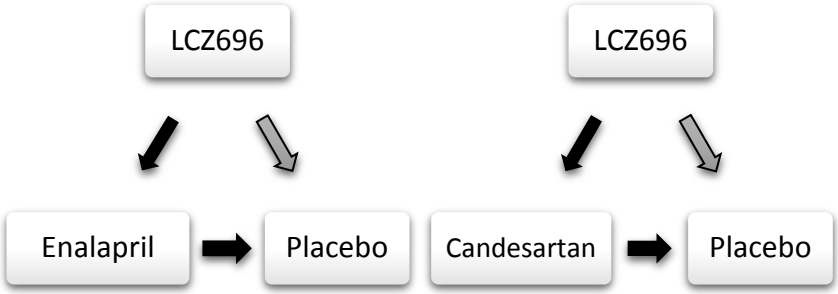
Study Design:

The design of this study used previously completed trials to assess the effects of LCZ696 to putative placebos.
The Studies of Left Ventricular Dysfunction (SOLVD-T) was used as a reference for comparing an ACE inhibitor to placebo.
The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity – Alternative trial (CHARM-Alternative) was used as reference for comparing an ARB and

placebo.
These treatment arms were then indirectly compared to results of LCZ696 found in the PARADIGM-HF study.

Description:

Although active-controlled trials with renin–angiotensin inhibitors are ethically mandated in heart failure with reduced ejection fraction, clinicians and regulators often want to know how the experimental therapy would perform compared with placebo. In attempts to compare LCZ696 with placebo, this study utilized the PARADIGM-HF data to make indirect comparisons of the effects of LCZ696 with putative placebos from previously completed trials. The hazard ratio of LCZ696 vs. a putative placebo was estimated through the product of the hazard ratio of LCZ696 vs. enalapril (active-control) and that of the historical active-control (enalapril or candesartan) vs. placebo. For the primary composite outcome of cardiovascular death or heart failure hospitalization in PARADIGM-HF, the relative risk reduction with LCZ696 vs. a putative placebo from SOLVD-T was 43% (95%CI 34–50%; $P < 0.0001$) with similarly large effects on cardiovascular death (34%, 21–44%; $P < 0.0001$) and heart failure hospitalization (49%, 39–58%; $P < 0.0001$). For all-cause mortality, the reduction compared with a putative placebo was 28% (95%CI 15–39%; $P < 0.0001$). Putative placebo analyses based on CHARM-Alternative gave relative risk reductions of 39% (95%CI 27–48%; $P < 0.0001$) for the composite outcome of cardiovascular death or heart failure hospitalization, 32% (95%CI 16–45%; $P < 0.0001$) for cardiovascular death, 46% (33–56%; $P < 0.0001$) for heart failure hospitalization, and 26% (95%CI 11–39%; $P < 0.0001$) for all-cause mortality.



Limitations:

The most obvious limitation of this article is the study design. As stated, it is unethical to utilize a placebo in the heart failure population, therefore an indirect comparison is necessary. However this introduces multiple variabilities within the sample population and forces the authors to make generalizations when evaluating data, of which cannot all be accounted for. These uncertainties make the exact strength of the study and the results difficult to assess. Additionally, each respective study contained conflicts of interests through manufacture funding, author employment and/or research support.

Conclusion:

With the limitations aside, these indirect comparisons of LCZ696 with a putative placebo did seem to show that the strategy of combined angiotensin receptor blockade and neprilysin inhibition led to striking reductions in cardiovascular and all-cause mortality, as well as heart failure hospitalization. These benefits were obtained even though LCZ696 was added to comprehensive background beta-blocker and mineralocorticoid receptor antagonist therapy.

Contraindications[1,2,3,4]:

Hypersensitivity to sacubitril or valsartan.

History of angioedema related to previous ACE or ARB therapy.

Use within 36 hours before or after a previous dose of an ACE inhibitor.

Co-administration of aliskiren in patients diabetic patients with renal impairment (eGFR <60 ml/min/1.73m^2).

Patients who are pregnant or plan to become pregnancy.

Precautions[1,2,3,4]:

Use with caution in patients having previous episodes of…

Angioedema – May occur, including laryngeal edema that may be fatal. Higher incidence in black patients and those with a past history of angioedema.

Hyperkalemia – May occur, especially in patients already at risk. Dose reduction or treatment interruption may be required.

Hypotension and/or Aortic/mitral stenosis – Hypotension incidents have been reported as a common adverse effect. Dose reduction or interruption in therapy may be warranted. Additionally, volume or salt depletion may increase risk of hypotension. Monitor patients until a stable dose is achieved.

Renal function deterioration – Increased risk of oliguria, progressive azotemia, acute renal failure and/or death in patients whose renal function is dependent on the renin-angiotensin system. Increased serum creatinine or BUN has also been observed in patients with unilateral or bilateral renal artery stenosis. Monitor patients and adjust as necessary

Heart failure – Monitor patients until a tolerated dose has been established

Hepatic impairment – Monitor patients and dose adjust as necessary.

Adverse Effects[1,2,3,4]:

>10%

Cardiovascular: Hypotension (18%).

Endocrine & metabolic: Hyperkalemia (12%).

Renal: a >50% increase in serum creatinine (16%).

1% - 10%

Cardiovascular: Orthostatic hypotension (2%).

Central nervous system: Dizziness (6%), falling (2%).

Hematologic & oncologic: Decreased hematocrit (<5%), decreased hemoglobin (<5%).

Hypersensitivity: Angioedema (Black patients 2%, others <1%).

Renal: Renal failure (5%).

Respiratory: Cough (9%).

Drug interactions[1,2,3,4]:

Angiotensin-converting enzyme inhibitors (ACE inhibitors)

Have been found to significantly increase Entresto's risk of angioedema. Additionally, compound effect with valsartan can increase risk of hypotension, syncope, hyperkalemia, changes in renal function, and acute kidney failure in some cases. Avoid combination and do not administer Entresto within 36 hours of switching to or from an ACE.

Angiotensin II receptor antagonists (ARBs)

Duplicate therapy. May result in increased risk of hypotension, syncope, hyperkalemia, changes in renal function, and acute kidney failure in some cases.

Aliskiren

Concurrent use may result in increased risk of hyperkalemia, renal impairment, and hypotension.

Potassium sparing diuretics, potassium supplements, or salt substitutes containing potassium

Increases serum potassium and may result in hyperkalemia.

Nonsteroidal anti-inflammatory drugs (NSAIDs) including selective Cyclooxygenase-2 Inhibitors (COX-2 inhibitors)

In elderly patients, patients who are volume depleted, or patients with preexisting renal insufficiency, co-administration with Entresto may cause worsening of renal function, including possible acute renal failure. Monitor renal function periodically.

Lithium

Lithium toxicity has been reported with co-administration of Entresto. Monitor serum lithium levels.

Dosing[2,3,4]:

Usual Dose:

Initial dose if not currently taking an ACE or ARB: sacubitril 24mg / valsartan 26mg.

Initial dose if currently switching from an ACE or ARB: sacubitril 49mg / valsartan 51mg.

Maintenance dose: double dose every 2 to 4 weeks until target dose of sacubitril 97mg / valsartan 103mg twice daily, or as tolerated.

Geriatric Dose:

Consider initial dose of sacubitril 24mg / valsartan 26mg. Increase over 2 to 4 weeks until target dose of sacubitril 97mg / valsartan 103mg twice daily, or as tolerated.

Pediatric Dose:

Safety and efficacy has not been evaluated in pediatric patients.

Dosing in renal impairment:

For severe renal impairment (eGFR < 30 ml/min/1.73m^2), consider initial dose of sacubitril 24mg / valsartan 26mg. Increase over 2 to 4 weeks until target dose of sacubitril 97mg / valsartan 103mg twice daily, or as tolerated.

No adjustment needed for mild to moderate renal impairment (eGFR > 30 ml/min/1.73m^2).

Dosing in hepatic impairment:

Not recommended in severe hepatic impairment (Child-Pugh class C).

For mild to moderate hepatic impairment (Child-Pugh class B), consider initial dose of sacubitril 24mg / valsartan 26mg. Increase over 2 to 4 weeks until target dose of sacubitril 97mg / valsartan 103mg twice daily, or as tolerated.

No adjustment needed for mild hepatic impairment (Child-Pugh class A).

Over dosage:

Limited data is available with regard to over dosage in human subjects with Entresto. In healthy volunteers, a single dose of 583mg sacubitril / 617mg valsartan, and multiple doses of 437mg sacubitril / 463 mg valsartan over 14 days, have been studied and were well tolerated. If overdose does become an issue, hypotension is most likely the result. Symptomatic treatment should be provided.

Use in special populations [1,2,3,4]:

Pregnancy

Entresto can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. 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

Lactation

It is unknown if sacubitril or valsartan can be found significantly in breast milk. Due to serious adverse effects in the nursing infant, breast feeding is not recommended by the manufacturer.

QTC Prolongation

In a thorough QTC clinical study in healthy male subjects, single dose 194 mg sacubitril / 206 mg valsartan, as well as 583mg sacubitril / 617mg valsartan had no effect on cardiac repolarization.

Conclusions:

Entresto is a combination product of sacubitril and valsartan indicated for the treatment of NYHA Class II or III heart failure patients with reduced ejection fraction. Its dual action has been shown to significantly reduce the risk of death with heart failure and to reduce the need for hospitalizations in this population. These benefits were shown to be greater than current standard therapy of an ACE inhibitor in combination with other medications such as beta blockers. These outcomes are due to Entresto's ability to relax blood vessels, making it easier for the heart to pump blood, and by helping the body retain less water. When switching to Entresto, it is important to follow a recommended washout period and titration schedule as appropriate to avoid serious adverse effects. Previous neprilysin inhibitors have failed to come to market due to significant angioedema. Although a much lower risk, Entresto still carries a concern for angioedema and should be taken into consideration when switching to or starting the medication. Entresto should also be used with caution in patients with severe kidney or liver disease, have ever had past issues with angioedema, have had previous hypotensive events, or those that have experienced potassium imbalances.
Entresto has not yet been placed into current guidelines, however many believe that this novel mechanism of action will come to replace first line treatments (ACE or ARB). As the previously mentioned trials have displayed some limitations, more data will need to be evaluated before confirming or denying its potential.

Recommended References:

1. Entresto [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2015
2. Entresto. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Hudson, OH. Available at: http://online.lexi.com. Accessed January 26, 2016.
3. Entresto. Micromedex 2.0. Truven Health Analytics, Inc. Greenwood Village, CO. Available at: http://www.micromedexsolutions.com. Accessed January 26, 2016.
4. Gold Standard, Inc. An Overview of Neurontin. Clinical Pharmacology [database online]. Available at: http://www.clinicalpharmacology.com. Accessed: January 26, 2016.

5. Solomon, Scott D., Michael Zile, and Burkert Pieske. "The Angiotensin Receptor Neprilysin Inhibitor LCZ696 in Heart Failure with Preserved Ejection Fraction: A Phase 2 Double-blind Randomised Controlled Trial." *The Lancet* 380.9851 (2012): 1387-395. Web.
6. Voors, Adriaan A., Mauro Gori, and Licette C.y. Liu. "Renal Effects of the Angiotensin Receptor Neprilysin Inhibitor LCZ696 in Patients with Heart Failure and Preserved Ejection Fraction." *Eur J Heart Fail European Journal of Heart Failure* 17.5 (2015): 510-17. Web
7. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993–1004.
8. Mcmurray, J., M. Packer, and A. Desai. "A Putative Placebo Analysis of the Effects of LCZ696 on Clinical Outcomes in Heart Failure." *European Heart Journal* 36.7 (2014): 434-39. Web.

Prepared by: Gary VanDyne, Doctor of Pharmacy Candidate