FOR US MEDIA ONLY

ENTRESTO ™ (SACUBITRIL/VALSARTAN) FACT SHEET

About Entresto

Entresto™ (sacubitril/valsartan) tablets, previously known as LCZ696, is indicated to reduce the risk of cardiovascular (CV) death and hospitalization for heart failure in patients with chronic heart failure (NYHA class II-IV) and reduced ejection fraction. It is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.[1] Entresto was approved by the U.S. Food and Drug Administration (FDA) in July 2015, making it the first and only heart failure medicine to demonstrate superiority over ACE-inhibitor enalapril, a guideline-recommended therapy that has been used for decades to treat heart failure with reduced ejection fraction.[1-4]

Entresto is a combination of a neprilysin inhibitor (sacubitril) and an angiotensin receptor blocker (valsartan) and reduces the strain on the failing heart. Entresto works by enhancing the protective neurohormonal systems of the heart (NP system) while simultaneously suppressing the harmful effects of the overactive renin-angiotensin-aldosterone system (RAAS).[1] Other available medicines only block the harmful effects of the overactive RAAS.[2]

Entresto film-coated tablets are available in three dosage strengths: 24/26 mg, 49/51 mg and 97/103 mg (sacubitril/valsartan). The target dose of Entresto is 97/103 mg twice daily.[1]

Entresto Clinical Data

The efficacy and safety of Entresto was evaluated in the largest clinical trial ever conducted in heart failure, the Phase III PARADIGM-HF study:[1,5]

- PARADIGM-HF was a multinational, randomized, double-blind, Phase III study comparing Entresto to enalapril in more than 8,400 patients with chronic heart failure (NYHA class II–IV) and systolic dysfunction (left ventricular ejection fraction ≤ 40%). Patients received Entresto or enalapril (each twice daily) in addition to current best treatment for a median duration of 27 months.
- Entresto demonstrated clinically relevant and statistically significant superiority to enalapril, reducing the risk of CV death or heart failure hospitalization by 20 percent (the primary endpoint). This result was consistent across the subgroups examined.
- Entresto also improved overall survival by 16 percent compared with enalapril, driven by a lower incidence of CV death.
- The most common adverse events occurring in patients taking Entresto (≥5%) were hypotension, hyperkalemia, cough, dizziness and renal failure.

PARADIGM-HF was initiated in December 2009, and in March 2014 the Data Monitoring Committee confirmed that patients given Entresto were significantly less likely to die from CV causes and that the primary endpoint had been met, which led the Committee to recommend that the trial be stopped early.[6]

Important Safety Information for Entresto

Entresto can harm or cause death to an unborn baby. Patients should talk to their doctor about other ways to treat heart failure if they plan to become pregnant. If a patient gets pregnant while taking Entresto, she should tell her doctor right away.

Patients are not to take Entresto if they are allergic to sacubitril or valsartan or any of the ingredients in Entresto; have had an allergic reaction including swelling of the face, lips, tongue, throat or trouble breathing while taking a type of medicine called angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB); or take an ACE inhibitor medicine. Patients are not to take Entresto for at least 36

hours before or after they take an ACE inhibitor medicine. Patients should talk with their doctor or pharmacist before taking Entresto if they are not sure if they take an ACE inhibitor medicine. Patients are not to take Entresto if they have diabetes and take a medicine that contains aliskiren.

Before they take Entresto, patients should tell their doctor about all of their medical conditions, including if they have kidney or liver problems; are pregnant or plan to become pregnant; are breastfeeding or plan to breastfeed. Patients should either take Entresto or breastfeed. They should not do both.

Patients should tell their doctor about all the medicines they take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. They should especially tell their doctor if they take potassium supplements or a salt substitute; nonsteroidal anti-inflammatory drugs (NSAIDs); lithium; or other medicines for high blood pressure or heart problems such as an ACE inhibitor, ARB, or aliskiren.

Entresto may cause serious side effects including serious allergic reactions causing swelling of the face, lips, tongue, and throat (angioedema) that may cause trouble breathing and death. Patients are to get emergency medical help right away if they have symptoms of angioedema or trouble breathing. Patients are not to take Entresto again if they have had angioedema while taking Entresto. People who are black or who have had angioedema may have a higher risk of having angioedema if they take Entresto. Entresto may cause low blood pressure (hypotension). Patients are to call their doctor if they become dizzy or lightheaded, or they develop extreme fatigue. Entresto may cause kidney problems or an increased amount of potassium in the blood.

The most common side effects were low blood pressure, high potassium, cough, dizziness, and kidney problems.

Please see full Prescribing Information, including Boxed WARNING, available at http://www.pharma.us.novartis.com/product/pi/pdf/entresto.pdf.

Patients are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

References:

1. Entresto Prescribing Information.
2. 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. *Circulation*. 2013;128:e240-e327.
3. McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993-1004. doi: 10.1056/NEJMoa1409077.
4. Merck. Merck 's First Quarter Earnings Per Share Increase 15%. http://www.thefreelibrary.com/Merck's+First+Quarter+Earnings+Per+Share+Increase+15%25.-a054450164. Published April 23, 1999. Accessed June 30, 2015.
5. McMurray JJV, Packer M, Desai AS, et al. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). *Eur J Heart Fail*. 2013;15:1062-73. doi:10.1093/eurjhf/hft052.
6. Novartis. PARADIGM-HF trial of Novartis' LCZ696 for chronic heart failure closes early based on strength of interim results. Novartis Newsroom. http://www.novartis.com/newsroom/media-releases/en/2014/1772754.shtml. Published March 31, 2014. Accessed June 30, 2015.