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Entresto - A Drug for the Treatment of Heart Failure-A Review

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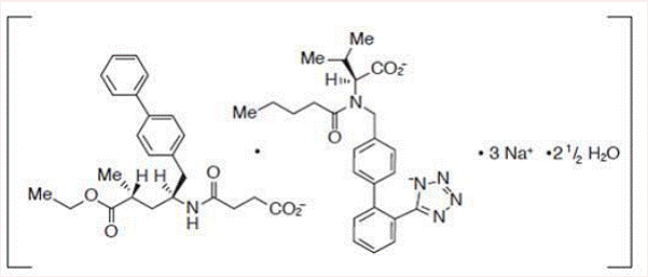
ABSTRACT

ENTRESTO (Sacubitril and Valsartan) is a combination of neprilysin inhibitor and an angiotensin 2 receptor blocker. ENTRESTO contains a complex comprised of anionic forms of sacubitril and valsartan, sodium cations, and water molecules. Following oral administration, the complex dissociates into Sacubitril (which is further metabolized to LBQ657) and valsartan. Its empirical formula (hemipentahydrate) is $C_{48}H_{55}N_6O_8Na_3 2.5H_2O$.Its molecular mass is 957.99 and its schematic structural formula is:



ENTRESTO is available as film-coated tablets for oral administration, containing 24 mg of sacubitril and 26 mg of valsartan; 49 mg of sacubitril and 51 mg of valsartan; and 97 mg of sacubitril and 103 mg of valsartan. The tablet inactive ingredients are microcrystalline cellulose, low-substituted hydroxypropyl cellulose, crospovidone, magnesium stearate (vegetable origin), talc, and colloidal silicon dioxide. [14, 6]

INTRODUCTION

Congestive heart failure is the physiological state in which cardiac output is insufficient to meet the needs of the body and the lungs. [123]

It is divided into two types: [9]

- Heart failure due to reduced ejection fraction/ also known as heart failure due to ventricular systolic dysfunction or systolic heart failure.

- Heart failure with preserved ejection fraction also known as diastolic heart failure or heart failure with normal ejection fraction.

The cardiac output is determined by preload, myocardial contractility, afterload.

Among the techniques used to assess the global cardiac function, the most clinically convenient is the evaluation of left ventricular ejection fraction, the ratio of the stroke volume to the end-diastolic volume of the left ventricle. Alternatively, in a patient in clinical heart failure; a normal or almost normal LVEV indicates diastolic heart failure.

SYMPTOMS

Left-sided heart failure: causes blood to back up into the lungs, causing respiratory symptoms (increased rate of breathing).

Right-sided heart failure: causes the backward failure of right ventricle leads to congestion of systemic capillaries, causes swelling under the skin called peripheral edema.

PATHOPHYSIOLOGY

The mechanisms involved are:

- Increase in diastolic tension

- Activation of the adrenergic system

- Activation of the RAAS system

- Atrial stretch stimulating secretion of atrial natriuretic peptide – ANP

- Release of endothelin

CAUSES [12, 13, 14]

- Coronary heart disease
- Diabetes
- Kidney disease
- Cardiomyopathy
- High BP

CLASSIFICATION

CLASS 1: no limitation is experienced in any activities; there are no symptoms from ordinary activities.

CLASS 2: slight, mild limitation of activity; the patient is comfortable at rest or with mild exertion.

CLASS 3: marked limitation of any activity; the patient is comfortable only at rest.

CLASS 4: any physical activity brings on discomfort and symptoms occur at rest.

CLINICAL PRESENTATIONS

- Shortness of breath
- Fatigue and weakness
- Swelling in your legs, ankles, and feet
- Lack of appetite and nausea
- Rapid or irregular heartbeat
- Reduced ability to exercise

DIAGNOSIS [8]

- Imaging: echocardiography is commonly used to support a clinical diagnosis of heart failure. This modality uses ultrasound to determine the stroke volume, the end-diastolic volume.

- Blood tests

- Angiography

TREATMENT [8]

Treatment focuses on improving the symptoms and preventing the progression of the disease. Reversible causes of heart failure also need to be addressed (infection, arrhythmia, and hypertension). Treatments include lifestyle and pharmacological modalities and occasionally various forms of device therapy and rarely cardiac transplantation.

DRUGS

- ACE INHIBITORS: captopril, enalapril, lisinopril, ramipril
- ARBs: candesartan, losartan, valsartan
- BETA BLOCKERS**:** carvedilol, metoprolol
- ALDOSTERONE ANTAGONIST: spironolactone
- COMBINATION DRUG**:** furosemide, indopamide, chlorthalidone

ENTRESTO [4]

FDA Approved: Yes (First approved July 7, 2015.

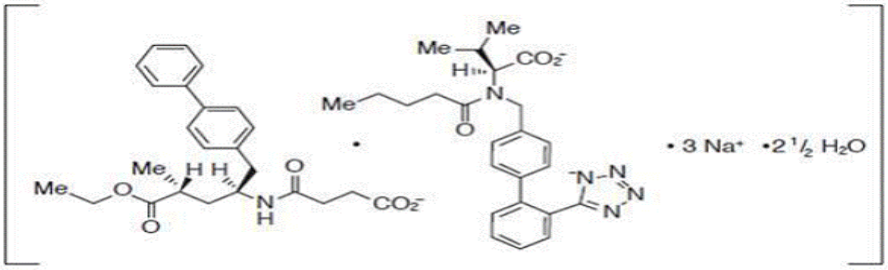
FDA Approved: Pediatric Heart Failure (October1 2019)

Brand name: Entresto

Previous Name: LCZ696

Generic name: sacubitril and valsartan

Company: Novartis Pharmaceuticals Corporation



DATE	ARTICLE
Oct 1, 2019	FDA approves entresto for pediatric heart failure.
Jul 7, 2015	FDA approves entresto (sacubutril / valsartan) for heart failure.
Feb 13, 2015	Novartis' heart failure medicine LCZ696 granted FDA priority review.
Nov 17, 2014	Nine new analysis show Novartis'LCZ696 could change the course of heart failure for patients.
Aug 30, 2014	Novartis'new heart failure medicine LCZ696 cut cardiovascular deaths by 20%vs. ACE inhibitor in landmark PARADIGM-HF trial.
Aug 27, 2012	New Novartis Phase 2 data show LCZ696 may provide clinical benefits in patients with a difficult-to-treat form of heart failure.

MECHANISM OF ACTION:

Entresto is the first-in-class angiotensin receptor neprilysin inhibitor (ARNI) that reduces strain on the failing heart. It contains two active components known as sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin receptor blocker.

The drug inhibits neprilysin and blocks angiotensin II type-I receptor. It increases the levels of peptides that are degraded by neprilysin.

Valsartan inhibits the effects of angiotensin II by blocking the AT1 receptor and by inhibiting the release of angiotensin II-dependent aldosterone.

PHARMACOKINETICS [6]

Absorption

Entresto dissociates into sacubitril and valsartan. Sacubitril further metabolized to LBQ657. Peak Plasma concentration of sacubitril LBQ657 and valsartan are reached in 0.5 hrs, 2 hrs, and 1.5 hrs. The oral absolute bioavailability of sacubitril is estimated to be >60%. Following twice-daily dosing of entries to, steady-state levels of sacubitril, LBQ657, and valsartan are reached in 3 days. Enter to administration with food has no clinically significant effect on systemic exposures of sacubitril, IBQ657 or Valsartan. **Entresto can be administered with or without food.**

Distribution: Sacubitril, LBQ657, and valsartan are highly bound to plasma proteins (94% to 97%). Based on the comparison of plasma and CSF exposures, LBQ657 crosses the blood-brain barrier to a limited extent (0.28%). The average apparent volumes of distribution of valsartan and sacubitril are 75 and 103 L, respectively.

Metabolism: Sacubitril is readily converted to LBQ657 by esterases; LBQ657 is not further metabolized to a significant extent. Valsartan is minimally metabolized; only about 20% of the dose is recovered as metabolites. A hydroxyl metabolite has been identified in plasma at low concentrations (< 10%).

Elimination: Following oral administration, 52% to 68% of sacubitril (primarily as LBQ657) and ~ 13% of valsartan and its metabolites are excreted in urine; 37% to 48% of sacubitril (primarily as LBQ657), and 86% of valsartan and its metabolites are excreted in feces. Sacubitril, LBQ657, and valsartan are eliminated from plasma with a mean elimination half-life (T1/2) of approximately 1.4 hours, 11.5 hours, and 9.9 hours, respectively.

PHARMACODYNAMICS [6]

The pharmacodynamic effects of ENTRESTO were evaluated after single and multiple-dose administrations in healthy subjects and patients with heart failure, and are consistent with simultaneous neprilysin inhibition and renin-angiotensin system blockade. In a 7-day valsartan-controlled study in patients with reduced ejection fraction (HFrEF), the administration of ENTRESTO resulted in a significant non-sustained increase in natriuresis, increased urine cGMP, and decreased plasma MR-proANP and NT-proBNP compared to

valsartan. ENTRESTO also blocked the AT1-receptor as evidenced by increased plasma renin activity and plasma renin concentrations. In PARADIGM-HF, ENTRESTO decreased plasma NTproBNP (not a neprilysin substrate) and increased plasma BNP (a neprilysin substrate) and urine cGMP compared with enalapril. In a thorough QTc clinical study in healthy male subjects, single doses of ENTRESTO 194 mg sacubitril/206 mg valsartan and 583 mg sacubitril/617 mg valsartan did not affect cardiac repolarization. Administration of ENTRESTO 194 mg sacubitril/206 mg valsartan once-daily for 2 weeks to healthy subjects was associated with an increase in CSF Aβ1-38 compared to placebo. Blood Pressure: Addition of a 50 mg single dose of sildenafil to ENTRESTO at steady state (194 mg sacubitril/206 mg valsartan once daily for 5 days) in patients with hypertension was associated with additional blood pressure (BP) reduction (~ 5/4 mmHg, systolic/diastolic BP) compared to administration of ENTRESTO alone. Co-administration of ENTRESTO did not significantly alter the BP effect of intravenous nitroglycerin.

ADVERSE DRUG REACTION [11]

- Hyperkalemia
- Hypotension
- Angioedema and impaired renal function

DOSES [11]

Sacubitril/valsartan, **film-coated tablet**

- 24mg/26mg
- 49mg/51mg
- 97mg/103mg

Heart Failure

Indicated to reduce the risk of cardiovascular death and hospitalization in chronic heart failure (CHF) (NYHA class II-IV) and reduced ejection fraction.

Recommended starting dose: 49 mg/51 mg PO BID

Target maintenance dose: After 2-4 weeks, double the dose to 97 mg/103 mg PO BID as tolerated

Dosage Modifications

Patients not taking an ACE inhibitor or other ARB, or previously taking a low dose of these agents when initiating treatment

- Reduce starting dose to 24 mg/26 mg BID.
- Double the dose every 2-4 weeks to target maintenance dose of 97 mg/103 mg BID as tolerated.

Renal impairment

- Mild-to-moderate (eGFR ≥30 mL/min/1.73 m²): No starting dose adjustment required.
- Severe (eGFR <30 mL/min/1.73 m²): Reduce starting dose to 24 mg/26 mg BID; double the dose every 2-4 weeks to target maintenance dose of 97 mg/103 mg BID as tolerated

Hepatic impairment

- Mild (Child-Pugh A): No starting dose adjustment required.
- Moderate (Child-Pugh B): Reduce starting dose to 24 mg/26 mg BID; double the dose every 2-4 weeks to target maintenance dose of 97 mg/103 mg BID as tolerated
- Severe (Child-Pugh C): Not recommended

Dosing Considerations

Contraindicated with concomitant use of an ACE inhibitor; if switching from an ACE inhibitor to sacubitril/valsartan, allow a washout period of 36 hr between administration of the 2 drugs

Usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB

OVERDOSAGE

Hypotension is the most likely result of overdosage due to the blood-pressure-lowering effects of entries too. Symptomatic treatment should be provided. Entresto is unlikely to be removed by hemodialysis because of high protein binding.

CONTRAINDICATIONS

- Patients with hypersensitivity to any component
- With concomitant use of aliskiren in patients with diabetes
- Patients with a history of angioedema related to previous ACE inhibitor /ARB therapy
- Pregnancy
- Liver problems
- Hepatic impairment
- Renal impairment

DRUG INTERACTIONS

Entresto + ACE is caused by an increased risk of angioedema.

Entresto + ARB (avoid the use)

Entresto + potassium-sparing diuretics causes an increase in serum potassium.

Entresto + lithium causes toxicity.

Entresto + NSAIDs causes acute renal failure.

PRECAUTIONS

Feel toxicity: entries to cause fetal harm when administered to a pregnant woman. When pregnancy is detected, consider alternative drug treatment and discontinue entries.

Angioedema: entres to should not be used in patients with a known history of angioedema related to previous ACE inhibitor or ARB.

Hypotension: entries to lower bp and may cause symptomatic hypotension.

STORAGE AND HANDLING[15]

Entresto is available as unscored, ovaloid, biconvex, film-coated, containing 24mg of sacubitril and 26mg of valsartan; 49mg of sacubitril and 51mg of valsartan; and 97mg of sacubitril and 103mg of valsartan. Store at 25 degrees Celsius with excursions between 15 and 30 degrees Celsius permitted. Protect from moisture,

CONCLUSION

Entresto (sacubitril and valsartan) is a neprilysin inhibitor and angiotensin2 receptor blocker combination. Entresto is the first treatment that shows a significant mortality benefit over an ACE-inhibitor; with data from the 8,442 patient PARADIGM-HF demonstrating that it cut cardiovascular deaths by 20% versus enalapril, as well as heart failure hospitalizations and all-cause mortality by 21% and 16% respectively. Angioedema has been reported as a serious side effect of entresto and patients are advised to seek emergency medical assistance if they experience symptoms such as trouble breathing. Due to the decreased side effects, entresto is used for the treatment of pediatric heart failure.

Entresto is a first-class treatment option that has demonstrated a significant mortality benefit, including reducing the risk of sudden death versus, the current standard of care, inpatient with reduced ejection.

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