ENTRESTO®: Change the heart. Change heart failure.

Proven superior to enalapril (ACEi) in both the outpatient and inpatient settings

- In PARADIGM-HF, the largest outpatient HF trial ever conducted, ENTRESTO was proven superior to enalapril at reducing the risk of HF hospitalization or CV death[1,2]
  - In an exploratory analysis, ENTRESTO decreased NT-proBNP[1]
- In PIONEER-HF, ENTRESTO was superior to enalapril in reducing NT-proBNP in the inpatient setting[3]

Improvement in structure, function, and NT-proBNP

- In PROVE-HF, ENTRESTO patients showed correlation between improvement in parameters of cardiac remodeling and biomarker improvement[4]
  - Patients in PROVE-HF showed reverse cardiac remodeling correlated with reduction in NT-proBNP[4]

ENTRESTO improves QOL

- Patients taking ENTRESTO felt better than those taking enalapril based on the KCCQ-23 Clinical Summary Score[2,5]

Patients with HF need a **superior*** HF treatment.
Start ENTRESTO now as a **first choice** instead of an ACEi/ARB for your patients with systolic HF

*Vs enalapril.

PARADIGM-HF was a multinational, randomized, double-blind trial comparing ENTRESTO to enalapril in 8442 symptomatic (NYHA Class II–IV) adult systolic HF patients (LVEF ≤40%). After discontinuing their existing ACEi or ARB therapy, patients entered sequential single-blind run-in periods during which they received enalapril 10 mg BID, followed by ENTRESTO 100 mg (49/51 mg) BID, increasing to 200 mg (97/103 mg) BID. Patients who successfully completed the run-in periods were then randomized to receive either ENTRESTO 200 mg (97/103 mg) (n=4209) BID or enalapril 10 mg (n=4233) BID. The median follow-up duration was 27 months, and patients were treated for up to 4.3 years. For the primary end point, composite of CV death or first HF hospitalization, ENTRESTO was superior to enalapril ($P<0.0001$).[1]

PIONEER-HF was a multicenter, randomized, double-blind, active-controlled clinical trial of in-hospital initiation of ENTRESTO (n=440) compared with enalapril (n=441) among HF patients with reduced EF (LVEF ≤40%) who had been stabilized following admission for ADHF. At the primary efficacy outcome, time-averaged proportional change in NT-proBNP concentration from baseline through weeks 4 and 8, ENTRESTO was superior to enalapril ($P<0.001$).[3]

PROVE-HF was a 52-week, single-arm, prospective, open-label phase IV evaluation of 794 systolic HF patients (LVEF ≤40%) initiated on ENTRESTO. For the primary end point, change in NT-proBNP was correlated with change in cardiac remodeling parameters ($P<0.001$).[4]

PROVE-HF study limitations: Observational, single-group, open-label design. A broad range of factors may affect NT-proBNP concentrations besides cardiac remodeling. Multiple comparisons may have increased risk of type 1 error. Not all echocardiographic measurements were available at each time point. Race was investigator-determined, with potential risk for inaccuracy.[4]

PARADIGM-HF key secondary end point QOL analysis utilized the KCCQ-23, a measurement of health-related quality of life (HRQoL) assessing the following domains: physical limitation, symptom frequency, symptom burden, symptom stability, self-efficacy, social limitation, and quality of life. The KCCQ-23 CS represents the average of symptom (frequency and burden) and physical limitation domains.[2,5,6]

KCCQ limitations: Recall period for KCCQ is 2 weeks, rather than daily. Patients who do not perform activities because of conditions other than their HF will have missing scores for the physical limitation domain.[6,7]

Additional limitations of KCCQ analysis as utilized in PARADIGM-HF: Baseline KCCQ-CS was assessed at randomization. This may have resulted in higher baseline scores due to treatment during the run-in phase. Limited data exist assessing clinical meaningfulness of change scores in patients with relatively good baseline perceptions of HRQoL. Statistical analysis suggests that the difference between ENTRESTO and enalapril treatment arms may have been driven in part by the treatment effect on HF hospitalizations.[5]

ACEi=angiotensin-converting enzyme inhibitor; HF=heart failure; CV=cardiovascular; NT-proBNP=N-terminal pro–b-type natriuretic peptide; QOL=quality of life; KCCQ-23=Kansas City Cardiomyopathy Questionnaire-23; ARB=angiotensin II receptor blocker; NYHA=New York Heart Association; LVEF=left ventricular ejection fraction; BID=twice daily; EF=ejection fraction; ADHF=acute decompensated heart failure; CS=Clinical Summary Score; KCCQ=Kansas City Cardiomyopathy Questionnaire.

INDICATION

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.

ENTRESTO is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.

Please see additional Important Safety Information on next page, and click here for the full Prescribing Information, including Boxed WARNING.

IMPORTANT SAFETY INFORMATION

WARNING: FETAL TOXICITY

- **When pregnancy is detected, discontinue ENTRESTO as soon as possible**
- **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus**

NOVARTIS

Entresto®
(sacubitril/valsartan) tablets
24/26mg • 49/51mg • 97/103mg

More than half of ENTRESTO® patients pay no more than $10 per month[8]*

Cost[8,9]:

98% of Medicare Part D patients have preferred access and pay the lowest branded co-pay for ENTRESTO

79% of commercially insured patients have preferred access and pay the lowest branded co-pay for ENTRESTO

Commercially insured patients pay as little as **$10** for a **30-**, **60-**, or **90**-day supply with the use of the co-pay card†

*Including dual eligible and low income subsidy patients.

†Limitations apply. This offer is not valid under Medicare, Medicaid, or any other federal or state program. See other eligibility requirements and full terms and conditions.

IMPORTANT SAFETY INFORMATION (cont)

ENTRESTO is contraindicated in patients with hypersensitivity to any component. ENTRESTO is contraindicated in patients with a history of angioedema related to previous angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy.

ENTRESTO is contraindicated with concomitant use of ACE inhibitors. Do not administer within 36 hours of switching from or to an ACE inhibitor. ENTRESTO is contraindicated with concomitant use of aliskiren in patients with diabetes.

Angioedema: ENTRESTO may cause angioedema. Angioedema associated with laryngeal edema may be fatal. ENTRESTO has been associated with a higher rate of angioedema in Black patients and in patients with a prior history of angioedema. ENTRESTO should not be used in patients with hereditary angioedema. If angioedema occurs, discontinue ENTRESTO immediately, provide appropriate therapy, and monitor for airway compromise. ENTRESTO must not be re-administered.

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 (e.g., those being treated with high doses of diuretics), are at greater risk. Correct volume or salt depletion prior to administration of ENTRESTO or start at a lower dose. If hypotension persists despite dose adjustment of diuretics, concomitant antihypertensive drugs, and treatment of other causes of hypotension (e.g., hypovolemia) reduce the dosage or temporarily discontinue ENTRESTO. Permanent discontinuation of therapy is usually not required.

Impaired Renal Function: Decreases in renal function may be anticipated in susceptible individuals treated with ENTRESTO. In patients whose renal function depends upon the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), 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.

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. Avoid use with aliskiren in patients with renal impairment (eGFR <60 mL/min/1.73 m^2).

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs), including COX-2 inhibitors, with ENTRESTO may result in worsening of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically.

Hyperkalemia: Hyperkalemia may occur with ENTRESTO. 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.

Concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium.

ARBs: Avoid use of ENTRESTO with an ARB, because ENTRESTO contains the angiotensin II receptor blocker valsartan.

Lithium: Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists. Monitor serum lithium levels during concomitant use with ENTRESTO.

Common Adverse Events: In a clinical trial, the most commonly observed adverse events with ENTRESTO vs enalapril, occurring at a frequency of at least 5% in either group, were hypotension (18%, 12%), hyperkalemia (12%, 14%), cough (9%, 13%) dizziness (6%, 5%) and renal failure/acute renal failure (5%, 5%).

References: 1. ENTRESTO [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; October 2019. **2.** McMurray JJV, Packer M, Desai AS, et al; for the PARADIGM-HF Investigators and Committees. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med.* 2014;371(11):993-1004. **3.** Velazquez EJ, Morrow DA, DeVore AD, et al; for the PIONEER-HF Investigators. Angiotensin–neprilysin inhibition in acute decompensated heart failure. *N Engl J Med.* 2019;380(6):539-548. **4.** Januzzi JL Jr, Prescott MF, Butler J, et al; for the PROVE-HF Investigators. Association of change in N-terminal pro–b-type natriuretic peptide following initiation of sacubitril-valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction. *JAMA.* 2019;322(11):1085-1095. **5.** Lewis EF, Claggett BL, McMurray JJV, et al. Health-related quality of life outcomes in PARADIGM-HF. *Circ Heart Fail.* 2017;10(8):e003430. **6.** Spertus JA, Jones PG. Development and validation of a short version of the Kansas City cardiomyopathy questionnaire. *Circ Cardiovasc Qual Outcomes.* 2015;8(5):469-476. **7.** Kansas City Cardiomyopathy Questionnaire (KCCQ). Medical Device Development Tool (MDDT) Qualification Decision Summary. https://www.fda.gov/media/108301/download. Qualified October 19, 2017. Accessed July 2, 2019. **8.** Data on file. ENTRESTO Affordability. Data from May 2019 to October 2019. Novartis Pharmaceuticals Corp; January 3, 2020. **9.** Data on file. ENTRESTO Access. Data from November 2019 & January 2, 2020. Novartis Pharmaceuticals Corp; January 3, 2020.

If you have any questions relating to this communication from Novartis Pharmaceuticals Corporation, please call 1-888-NOW-NOVA (1-888-669-6682), Monday through Friday, 8:30 AM to 5:00 PM ET. You may also submit your question in writing to: Novartis Pharmaceuticals Corporation, One Health Plaza, Customer Interaction Center, East Hanover, NJ 07936-1080.

Please see additional Important Safety Information on previous page, and click here for the full Prescribing Information, including Boxed WARNING.

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East Hanover, New Jersey 07936-1080

3/20 T-ETR-1388240

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