In a study with a median follow-up of 27 months,

1 HOSPITALIZATION

put HFrEF patients at up to

6X GREATER RISK OF DEATH

vs those who had not been hospitalized for HFrEF[1,2]*

START ENTRESTO®

for HF patients with LVEF ≤60% to help reduce the risk of CV death and HF hospitalization

*Post hoc analysis of the PARADIGM-HF study, a multinational, randomized, double-blind trial comparing sacubitril/valsartan to enalapril in 8442 symptomatic (NYHA Class II–IV) HFrEF patients (LVEF ≤40%). For the primary end point, composite of CV death or first HF hospitalization, sacubitril/valsartan was superior to enalapril (*P*<.0001). This post hoc analysis examined the association of first nonfatal events—either HF hospitalization, ED visit, or outpatient intensification of HF therapy—with subsequent mortality during the trial. For the 1107 patients in the study who had a hospitalization for worsening HF as a first event, vs those with no event, the HR for mortality was 6.1 (95% CI: 5.4–6.8).

ED, emergency department; HR, hazard ratio; NYHA, New York Heart Association.

INDICATION

ENTRESTO is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal.

LVEF is a variable measure, so use clinical judgment in deciding whom to treat.

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**

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.

Please see additional Important Safety Information throughout and **tap here** for full Prescribing Information, including **Boxed WARNING**.

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

2022 AHA/ACC/HFSA HF Guideline recommended
ENTRESTO® has the STRONGEST CLASS OF RECOMMENDATION and is the preferred RASi instead of ACEi/ARB in HFrEF[3]*

HFrEF*
LVEF ≤40%

START

ENTRESTO is **strongly recommended** to reduce **MORBIDITY AND MORTALITY**

REPLACE

In patients with chronic symptomatic **HFrEF*** who tolerate an ACEi/ARB, **replacement with ENTRESTO is recommended** to further reduce **MORBIDITY AND MORTALITY**

(Class 1 recommendation)

HFmrEF
LVEF 41% to 49%

START

Consider ENTRESTO to **reduce** the risk of **HF HOSPITALIZATION AND CV MORTALITY**

(Class 2b recommendation)

HFpEF
LVEF ≥50%

START

Consider ENTRESTO to **decrease HF HOSPITALIZATIONS,** particularly for patients with LVEF on the lower end of the spectrum†

(Class 2b recommendation)

ENTRESTO IS THE FAVORED RASi IN THE 2023 ACC ECDP FOR HFpEF[4†]

The **2023 ACC ECDP for HFpEF favors the use of ENTRESTO instead of an ARB** for HFpEF patients with LVEF <55% to 60%, unless not feasible due to contraindication, cost, or intolerance.

*NYHA Class II–III patients with HFrEF.

†In PARAGON-HF, HFpEF was defined as LVEF ≥45% with structural heart disease (LAE or LVH) and no prior echocardiographic LVEF <40%. Median LVEF was 57%.[1,5]

ACC, American College of Cardiology; ACEi, angiotensin-converting enzyme inhibitor; AHA, American Heart Association; ARB, angiotensin II receptor blocker; ECDP, Expert Consensus Decision Pathway; HFmrEF, heart failure with mildly reduced ejection fraction; HFSA, Heart Failure Society of America; LAE, left atrial enlargement; LVH, left ventricular hypertrophy; RASi, renin-angiotensin system inhibitor.

IMPORTANT SAFETY INFORMATION (cont)

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.

Please see additional Important Safety Information throughout and **tap here** for full Prescribing Information, including **Boxed WARNING**.

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

ENTRESTO® can help keep your appropriate HF patients with LVEF ≤60% alive and out of the hospital[1,6,7]

DATA FROM 2 PIVOTAL TRIALS:

PARADIGM-HF

HFrEF patients with **LVEF ≤40%**[1,7]

20%
RELATIVE RISK REDUCTION

IN CV DEATH OR HF HOSPITALIZATION AS A FIRST EVENT (COMPOSITE END POINT) VS ENALAPRIL

HR 0.80 (95% CI: 0.73–0.87); 4.7% ARR, *P*<.0001
NNT: 21

In an exploratory analysis, ENTRESTO lowered NT-proBNP by 32% vs 7% with enalapril, compared to baseline (screening), at 4 weeks after randomization. NT-proBNP was analyzed in a subgroup and may not represent the full population. ENTRESTO CV effects are due to increased peptides and decreased angiotensin II effects, which result in decreased NT-proBNP.[1,8]

PARAGON-HF

Prespecified subgroup analysis of **HFpEF** patients with **LVEF ≤57%**[1,9]*

22%
RELATIVE RATE REDUCTION

IN TOTAL HF HOSPITALIZATIONS AND CV DEATH (COMPOSITE END POINT) VS VALSARTAN

RR 0.78 (95% CI: 0.64–0.95); 3.6 ARR†
Driven by reduction in HF hospitalizations

At the primary end point, a composite of total (first and recurrent) HF hospitalizations and CV death, ENTRESTO did not achieve statistical significance vs valsartan (RR 0.87; 95% CI: 0.75–1.01; *P*=.06).[1]

Please **tap here** for **PARADIGM-HF and PARAGON-HF study designs**.

Start Early. Start Now. Start ENTRESTO.

*LVEF is a variable measure that can change over time, and the normal range differs according to patient characteristics and method of assessment. In PARAGON-HF, the median LVEF was 57%.
†Event rate per 100 patient-years.

ARR, absolute risk reduction (PARADIGM-HF); ARR, absolute rate reduction (PARAGON-HF); NNT, number needed to treat; RR, rate ratio.

IMPORTANT SAFETY INFORMATION (cont)

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.

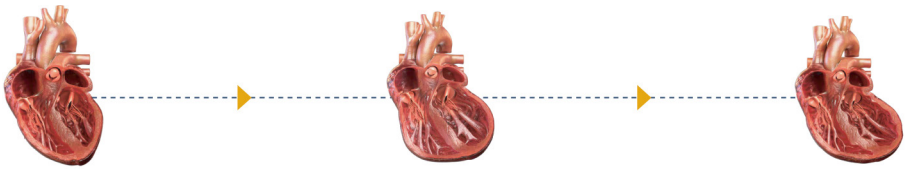
ENTRESTO may increase blood urea and serum creatinine levels in patients with bilateral or unilateral renal artery stenosis. In patients with renal artery stenosis, monitor renal function. Avoid use with aliskiren in patients with renal impairment (eGFR <60 mL/min/1.73 m^2).

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.

Please see additional Important Safety Information throughout and **tap here** for full Prescribing Information, including **Boxed WARNING**.

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

Cardiac remodeling leads to disease progression[10-15]



HEALTHY HEART

REMODELED HFrEF HEART

- HFrEF is a clinical syndrome caused by changes in cardiac structure and function
- These changes can include increased left atrial and ventricular volumes and filling pressure and decreased ejection fraction
- Cardiac remodeling leads to disease progression and increased risk of CV death and HF hospitalization

REVERSE CARDIAC REMODELING

- Reverse cardiac remodeling changes can include decreased left atrial and ventricular volumes and filling pressure and increased ejection fraction
- An association has been seen between reverse cardiac remodeling and NT-proBNP reduction

In HFrEF,

PROVE-HF: Reduction in NT-proBNP with ENTRESTO® significantly correlated with improved measures of cardiac structure and function[10]

PRIMARY END POINT: The correlation (Pearson *r*)* between change in echocardiographic remodeling parameters and NT-proBNP at 12 months (*P*<.001).

Functional measures included E/e': *r*=0.269 and LVEF: *r*=-0.381.
Structural measures included LAVI: *r*=0.263, LVEDVI: *r*=0.320, and LVESVI: *r*=0.405.

PROVE-HF: STUDY DESIGN

PROVE-HF was a 52-week, single-group, prospective, open-label Phase IV study of 794 adult HFrEF (LVEF ≤40%) outpatients initiated on ENTRESTO.

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

*A Pearson correlation coefficient (Pearson *r*) measures how strong the association is between 2 variables. It ranges from 1 (exactly correlated) to -1 (exactly inversely correlated).

E/e', filling pressure (early diastolic filling velocity/early diastolic mitral annular velocity); LAVI, left atrial volume index; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

IMPORTANT SAFETY INFORMATION (cont)

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.

Please see additional Important Safety Information throughout and **tap here** for full Prescribing Information, including **Boxed WARNING**.

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

ENTRESTO® supports your eligible heart failure patients with options to help them start and stay on treatment

FOR PATIENTS WITH MEDICARE

ENTRESTO is available at the lowest branded co-pay for more than 99% of eligible patients[16]

FOR ELIGIBLE COMMERCIALLY INSURED PATIENTS

May pay as little as a $10 co-pay for up to a 90-day supply of ENTRESTO*

THE ENSPIRE PROGRAM FROM ENTRESTO®†

Patients can sign up for this free 12-month lifestyle and treatment support program‡

FREE TRIAL OFFER AVAILABLE TO ALL PATIENTS§:

Regardless of insurance, patients can access a 30-day free trial offer, pre-activated and ready to use when initiating treatment

SCAN FOR MORE
patient support information and resources

FOR YOUR PATIENTS WITH LIMITED OR NO PRESCRIPTION COVERAGE, THEY MAY QUALIFY FOR HELP FROM NOVARTIS PATIENT ASSISTANCE FOUNDATION (NPAF)

NPAF is a non-profit entity within Novartis that supports access to prescribed Novartis medications for patients who have limited or no prescription coverage and cannot afford the cost of their medication. You can call NPAF at 1-800-277-2254 or visit www.PAP.Novartis.com for more information and to download an application.

Start Early. Start Now. Start ENTRESTO.

*Limitations apply. See Program Terms and Conditions. Eligible commercial patients pay as little as a $10 co-pay for each prescription fill (30-, 60-, 90-day fill) at retail or mail order. The program pays up to a $4100 cap across all fills per calendar year. Patient will be responsible for any co-pay once the $4100 limit is reached in a calendar year. This offer is not valid under Medicare, Medicaid, or any other federal or state program. See complete Terms and Conditions for details at EntrestoHCP.com/support-and-resources.

†Must be 18 or older to enroll in the ENSPIRE Program from ENTRESTO®.

‡Your patient can choose how they would like to be contacted, and they can opt out of any of these communications at any time.

§Limitations apply. This voucher is good for a 30-day (maximum 60 tablets; one-time use) free trial of ENTRESTO at no cost for your patient. Visit EntrestoHCP.com/support-and-resources to view Terms and Conditions.

IMPORTANT SAFETY INFORMATION (cont)

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.

Please see additional Important Safety Information throughout and **tap here** for full Prescribing Information, including **Boxed WARNING**.

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

From HFrEF to HFpEF in patients with LVEF ≤60%, make ENTRESTO® an ESSENTIAL part of your appropriate patients' heart failure treatment today

START EARLY: HELP KEEP APPROPRIATE PATIENTS ALIVE AND OUT OF THE HOSPITAL[1]

START NOW: REPLACE THE ACEi/ARB[1,3*†]
Strongest class of recommendation in HFrEF as a first-line treatment and is preferred instead of an ACEi/ARB in the 2022 HF Guideline
*When switching from an ACEi, be sure to allow for a 1.5-day washout period prior to initiating ENTRESTO.

START ENTRESTO AND EXPLORE PATIENT SUPPORT OPTIONS
to determine whether your patients are eligible for support to help them stay on ENTRESTO as prescribed

The #1 heart failure brand prescribed by cardiologists[17]

Start Early. Start Now. Start ENTRESTO.

Please **tap here** for **References**.

†In the 2022 HF Guideline, ENTRESTO is recommended as a first-line treatment and to replace well-tolerated ACEi/ARB in patients with NYHA Class II–III HFrEF (Class 1 recommendation). ENTRESTO was also included as a treatment option for HFmrEF (LVEF 41%–49%) and select patients with HFpEF (LVEF ≥50%), particularly for patients with LVEF on the lower end of the spectrum (Class 2b recommendation).

INDICATION

ENTRESTO is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal.

LVEF is a variable measure, so use clinical judgment in deciding whom to treat.

IMPORTANT SAFETY INFORMATION (cont)

Common Adverse Events: In a clinical trial of patients with heart failure with reduced ejection fraction, 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%). No new adverse reactions were identified in a trial of the remaining indicated population.

Please see additional Important Safety Information throughout and **tap here** for full Prescribing Information, including **Boxed WARNING**.

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080
© 2024 Novartis 1/24 394852

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

PARADIGM-HF: STUDY DESIGN[1]

PARADIGM-HF was a multinational, randomized, double-blind trial comparing ENTRESTO® to enalapril in 8442 symptomatic (NYHA Class II–IV) adult HFrEF patients (LVEF ≤40%). After discontinuing their existing ACEi or ARB therapy, patients entered sequential single-blind, run-in periods during which they received enalapril followed by ENTRESTO. Patients who successfully completed the run-in periods were then randomized to receive either ENTRESTO 200 mg BID (n=4209) or enalapril 10 mg BID (n=4233). The median follow-up duration was 27 months, and patients were treated for up to 4.3 years.

PARAGON-HF: STUDY DESIGN[1,5]

PARAGON-HF was a randomized, double-blind, active-controlled trial comparing ENTRESTO to valsartan in 4796 adult patients with symptomatic (NYHA Class II–IV) HFpEF (LVEF ≥45%, elevated levels of natriuretic peptides, structural heart disease [LAE or LVH], and no prior echocardiographic LVEF <40%). After completing the run-in period with valsartan, followed by ENTRESTO, patients entered the double-blind period and were randomly assigned (1:1) to ENTRESTO 97/103 mg BID (n=2407) or valsartan 160 mg BID (n=2389). The median follow-up duration was 35 months, and patients were treated for up to 4.7 years.

REFERENCES

1. ENTRESTO® [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp. **2.** Okumura N, Jhund PS, Gong J, et al. Importance of clinical worsening of heart failure treated in the outpatient setting: evidence from the prospective comparison of ARNi with ACEi to determine impact on global mortality and morbidity in heart failure trial (PARADIGM-HF). *Circulation*. 2016; 133(23):2254-2262. doi:10.1161/CIRCULATIONAHA.115.020729 **3.** Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines [published correction appears in *J Am Coll Cardiol*. 2023;81(15):1551]. *J Am Coll Cardiol*. 2022;79(17):e263-e421. doi:10.1016/j.jacc.2021.12.012 **4.** Kittleson MM, Panjrath GS, Amancherla K, et al. 2023 ACC expert consensus decision pathway on management of heart failure with preserved ejection fraction: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2023;81(18):1835-1878. doi:10.1016/j.jacc.2023.03.393 **5.** Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019;381(17):1609-1620. doi:10.1056/NEJMoa1908655 **6.** Vaduganathan M, Claggett BL, Greene SJ, et al. Potential implications of expanded US Food and Drug Administration labeling for sacubitril/valsartan in the US. *JAMA Cardiol*. 2021;6(12):1415-1423. doi:10.1001/jamacardio.2021.3651 **7.** McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993-1004. doi:10.1056/NEJMoa1409077 **8.** Data on file. LCZ696 Clinical Study Report (CLCZ696B2314). Novartis Pharmaceuticals Corp; 2014. **9.** US Food and Drug Administration. Novartis cardiovascular and renal drugs advisory committee briefing document, December 15, 2020. ENTRESTO® (sacubitril/valsartan) for chronic heart failure and preserved ejection fraction. Accessed December 8, 2023. http://web.archive.org/web/20221010233253/https://www.fda.gov/media/144379/download **10.** Januzzi JL Jr, Prescott MF, Butler J, et al. 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. doi:10.1001/jama.2019.12821 **11.** Daubert MA, Adams K, Yow E, et al. NT-proBNP goal achievement is associated with significant reverse remodeling and improved clinical outcomes in HFrEF. *JACC Heart Fail*. 2019;7(2):158-168. doi:10.1016/j.jchf.2018.10.014 **12.** Weiner RB, Baggish AL, Chen-Tournoux A, et al. Improvement in structural and functional echocardiographic parameters during chronic heart failure therapy guided by natriuretic peptides: mechanistic insights from the ProBNP Outpatient Tailored Chronic Heart Failure (PROTECT) study. *Eur J Heart Fail*. 2013;15(3):342-351. doi:10.1093/eurjhf/hfs180 **13.** Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling—concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. *J Am Coll Cardiol*. 2000;35(3):569-582. doi:10.1016/s0735-1097(99)00630-0 **14.** Konstam MA, Kramer DG, Patel AR, Maron MS, Udelson JE. Left ventricular remodeling in heart failure: current concepts in clinical significance and assessment. *JACC Cardiovasc Imaging*. 2011;4(1):98-108. doi:10.1016/j.jcmg.2010.10.008 **15.** Udelson JE, Konstam MA. Ventricular remodeling fundamental to the progression (and regression) of heart failure. *J Am Coll Cardiol*. 2011;57(13):1477-1479. doi:10.1016/j.jacc.2011.01.009 **16.** Data on file. Novartis Pharmaceuticals Corp; 2022. **17.** Data on file. IQVIA Xponent Data for Cardiologists; 2023.