ENTRESTO® has demonstrated a consistent renal safety profile in a broad range of patients with HF[1-3]

ACROSS 3 LANDMARK TRIALS, ENTRESTO DEMONSTRATED RENAL SAFETY SIMILAR TO ACEi/ARB[1-3]

PARADIGM-HF

Renal impairment was rarely the cause of stopping study medication in patients with HFrEF[1,4]

- Fewer patients in the **ENTRESTO** group (0.7%) stopped their study medication permanently because of renal impairment than in the enalapril group (1.4%)[1]
- Serum creatinine levels of 2.5 mg per deciliter (221 µmol per liter) or more were reported less frequently in the **ENTRESTO** group (3.3%) than in the enalapril group (4.5%)[1]

PARAGON-HF

Rates of renal impairment were similar to valsartan in patients with HFpEF* with an LVEF below normal[5†]

- Rates[‡] of renal adverse events were similar to that of the valsartan (ARB) active comparator in the subgroup of patients with LVEF ≤57%[5]
  - Renal impairment: 11.5% vs 15.4%[6]
  - AKI: 5.3% vs 5.4%[6]
  - Renal failure: 3.9% vs 5.2%[6]

HF patients with LVEF below normal need a treatment you can feel confident prescribing.

Start ENTRESTO now as a first choice instead of an ACEi/ARB for your patients.

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 either ENTRESTO 97/103 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. For the primary end point, composite of CV death or first HF hospitalization, ENTRESTO was superior to enalapril ($P<0.0001$). In an exploratory analysis, ENTRESTO also lowered NT-proBNP. The CV effects of ENTRESTO are attributed to increased levels of peptides and decreased angiotensin II effects, which resulted in decreased NT-proBNP.[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 HFrEF patients (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 ($P<0.001$).[2]

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 and structural heart disease. 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. For the primary end point, reduction in the composite of total (first and recurrent) HF hospitalizations and CV death, ENTRESTO did not achieve statistical significance vs valsartan (13% RRR; 95% CI: 0.75, 1.01; $P=0.06$).[3]

*The patient population of PARAGON-HF met the protocol definition of HFpEF with an LVEF ≥45%, structural heart disease (either LAE or LVH), and no prior echocardiographic LVEF <40%.

†The median LVEF was 57%. LVEF is a variable measure that can change over time, and the normal range differs according to patient characteristics and method of assessment.

‡A patient with multiple instances of an AE is counted once.

ACEi=angiotensin-converting enzyme inhibitor; ADHF=acute decompensated heart failure; AKI=acute kidney injury; ARB=angiotensin II receptor blocker; eGFR=estimated glomerular filtration rate; LAE=left atrial enlargement; LVEF=left ventricular ejection fraction; LVH=left ventricular hypertrophy; NT-proBNP=N-terminal prohormone of the brain natriuretic peptide; 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.

IMPORTANT SAFETY INFORMATION (cont)

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.

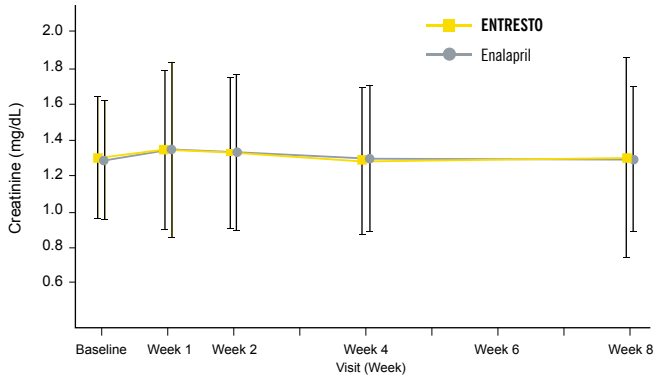
Entresto®
(sacubitril/valsartan) tablets
24/26mg · 49/51mg · 97/103mg

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

Across a diverse population, increase in serum creatinine did not differ significantly between ENTRESTO® and enalapril[2,4]

PIONEER-HF: SAFETY PROFILE

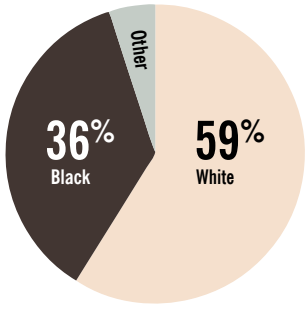
Mean creatinine by visit and treatment through Week 8 (safety set)[4]



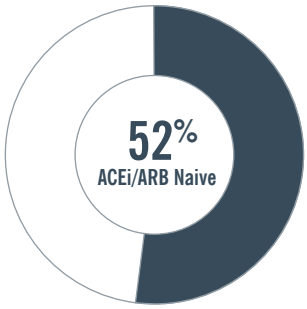
ENTRESTO - Total n:	421	403	389	379	369
Enalapril - Total n:	421	393	384	367	366

PIONEER-HF: SELECTED DEMOGRAPHIC INFORMATION

Patients enrolled in PIONEER-HF represented a diverse population with varying treatment history (N=881)[2]



Race



Treatment History

IMPORTANT SAFETY INFORMATION (cont)

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

References: 1. 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. **2.** 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. **3.** Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin–neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019;381(suppl):1609-1620. Accessed December 13, 2021. Supplementary material accessed at https://www.nejm.org/doi/suppl/10.1056/NEJMoa1908655/suppl_file/nejmoa1908655_appendix.pdf **4.** Supplement to: Velazquez EJ, Morrow DA, DeVore AD, et al. Angiotensin–neprilysin inhibition in acute decompensated heart failure. *N Engl J Med*. 2019;380:539-48. doi:10.1056/NEJMoa1812851 **5.** Supplement to: Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin–neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019;381:1609-20. doi:10.1056/NEJMoa1908655 **6.** Data on file. Novartis Pharmaceuticals Corp; January 2022.

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