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.

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

Please see additional Important Safety Information on pages 19–20, and click here for full Prescribing Information, including Boxed WARNING.
**Entresto™**
(sacubitril/valsartan) tablets
24/26mg - 49/51mg - 97/103mg

**SET A NEW STANDARD WITH ENTRESTO™:**

A novel treatment, with the first and only angiotensin II receptor blocker and neprilysin inhibitor combination. Proven superior to enalapril, a current standard-of-care medication,\(^2\) in reducing the risk of CV death and HF hospitalization.\(^1\)

HF = heart failure; CV = cardiovascular.

**IMPORTANT SAFETY INFORMATION, CONT’D**

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. If angioedema occurs, discontinue ENTRESTO immediately, provide appropriate therapy, and monitor for airway compromise. ENTRESTO must not be re-administered.

Please see additional Important Safety Information on pages 19–20, and click here for full Prescribing Information, including Boxed WARNING.
**ENTRESTO combines an ARB with the first and only neprilysin inhibitor**¹

In HF patients, some systems become stimulated, causing harmful effects, while others have beneficial effects³,⁴

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**HARMFUL EFFECTS**
- Vasoconstriction
- Fibrosis
- Sodium retention
- Hypertrophy

**OVERACTIVE RAAS³,⁴**

**BENEFICIAL EFFECTS**
- Vasodilation
- Natriuresis
- Renin suppression
- Aldosterone suppression
- Antifibrosis

**ENTRESTO**

**THE FIRST AND ONLY**

ARB and neprilysin inhibitor combination¹

**ENTRESTO not only inhibits the overactive RAAS, but also inhibits the breakdown of vasoactive peptides, such as natriuretic peptides¹**

Neprilysin breaks down compensatory endogenous peptides, including vasoactive peptides which have beneficial effects⁴,⁵

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**IMPORTANT SAFETY INFORMATION, CONT’D**

**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.

Please see additional Important Safety Information on pages 19–20, and click here for full Prescribing Information, including Boxed WARNING.
The landmark trial, PARADIGM–HF, provided evidence to support the replacement of ACE inhibitors with ENTRESTO in the management of chronic HFrEF\textsuperscript{1,6}

Results published in the *New England Journal of Medicine*

The PARADIGM–HF trial was the largest clinical trial ever conducted in HF\textsuperscript{7}

8442 PATIENTS WERE RANDOMIZED\textsuperscript{1}

- Head-to-head comparison: ENTRESTO (n=4209) vs enalapril (n=4233)
- NYHA class II–IV
  - 70% of study population were NYHA class II
  - NYHA class II is defined as having slight limitations of physical activity (comfortable at rest, but ordinary physical activity causes symptoms of HF)\textsuperscript{2}
- Systolic dysfunction with left ventricular ejection fraction ≤40%\textsuperscript{*}
- Patients in both arms were treated with evidence-based therapies, including beta-blockers (94%), diuretics (82%), and mineralocorticoid receptor antagonists (58%)
- The primary end point was the first event in the composite of CV death or hospitalization for HF
- Median duration of follow-up was 27 months, and patients were treated for up to 4.3 years

\textsuperscript{*}Later amended to ≤35%\textsuperscript{.4}

NYHA=New York Heart Association.

**IMPORTANT SAFETY INFORMATION, CONT’D**

Hypotension, cont’d: 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.

“We examined whether the... effects of LCZ696 [ENTRESTO] on [HF hospitalization] and mortality were superior to those of ACE inhibition with enalapril in patients with chronic heart failure and a reduced ejection fraction.”

The PARADIGM-HF trial was an outcomes-driven, head-to-head comparison vs enalapril, an evidence-based standard-of-care medicine\(^1\,^2\)

**Trial Design**\(^1\,^6\)

**SINGLE-BLIND RUN-IN PERIOD**
(6 TO 8 WEEKS)

- **MEDIAN EXPOSURE:**
  - 15 DAYS \((N=10,513)\)
  - 29 DAYS \((N=9419)\)

- **Enalapril**
  - 10 mg twice daily

- **ENTRESTO**
  - 49/51 (100 mg) twice daily
  - 97/103 (200 mg) twice daily

There were two 36-hour washout periods during the run-in period to minimize the potential risk of angioedema due to overlapping ACE-NEP inhibition—the first after completing the enalapril run-in period, and the second after completing the ENTRESTO run-in period.\(^6\)

**DOUBLE-BLIND PERIOD**
(STUDY DURATION WAS EVENT-DRIVEN)

- **ENTRESTO**
  - 97/103 (200 mg) twice daily
  - \(N=4209\)

- **(1:1 RANDOMIZATION)**

- **Enalapril**
  - 10 mg twice daily
  - \(N=4233\)

NEP = neutral endopeptidase (neprilysin)
*All patients were on an ACEi or ARB prior to the run-in period\(^1\)

**IMPAIRED SAFETY INFORMATION, CONT’D**

**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.

*Median follow-up duration was 27 months; patients were treated for up to 4.3 years\(^1\)
The PARADIGM–HF trial stopped early due to compelling efficacy\(^6\)

ENTRESTO was superior in reducing the relative risk of CV death or first HF hospitalization, and treatment effect reflected a reduction in both\(^1\)

20% REDUCED RISK OF CV DEATH OR HF HOSPITALIZATION AS FIRST EVENT vs ENALAPRIL\(^1\)

4.7% ABSOLUTE RISK REDUCTION\(^1\)

ENTRESTO demonstrated consistent efficacy on the primary end point across prespecified subgroups.\(^1\) To view the full ENTRESTO subgroup analysis, please visit EntrestoHCP.com

ENTRESTO delivered early and sustained relative risk reduction\(^6\)

**Time to First Occurrence of CV Death or HF Hospitalizations\(^1\)**

<table>
<thead>
<tr>
<th>Time since randomization (months)</th>
<th>KM estimate of cumulative failure rate (%)</th>
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<tbody>
<tr>
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**P < 0.0001**

HR (95% CI): 0.80 (0.73, 0.87)

**IMPORTANT SAFETY INFORMATION, CONT’D**

Impaired Renal Function, cont’d: Closely monitor serum creatinine, and down-titrator 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.
ENTRESTO was superior in reducing risk of CV death at any time, and in reducing risk of first HF hospitalization\(^{1\ast\dagger}\)

**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.

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**Important Safety Information, Cont’d**

HR (95% CI): 0.80 (0.71, 0.89)

**Time to Occurrence of CV Death**

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<th>KM estimate of cumulative failure rate (%)</th>
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**ENTRESTO**

**Enalapril**

**20%**

**Reduced Risk of CV Death** vs ENALAPRIL\(^{\dagger}\)

**3.2%**

**Absolute Risk Reduction**

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**Time to First Occurrence of HF Hospitalization**

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**ENTRESTO**

**Enalapril**

**21%**

**Reduced Risk of First HF Hospitalization** vs ENALAPRIL

**2.8%**

**Absolute Risk Reduction**

---

Please see additional Important Safety Information on pages 19–20, and click here for full Prescribing Information, including Boxed WARNING.
ENTRESTO improved overall survival by reducing the risk of CV death vs enalapril

ENTRESTO reduced mortality vs enalapril

16%
REDUCED RISK OF ALL-CAUSE MORTALITY vs ENALAPRIL

2.8%
ABSOLUTE RISK REDUCTION

IMPORTANT SAFETY INFORMATION, CONT’D

Hyperkalemia, cont’d: 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.

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Fewer patients taking ENTRESTO discontinued therapy due to an adverse event during the double-blind period (10.7% vs 12.2%):

- Discontinuation rates during the run-in periods were:
  - 5.6% enalapril
  - 5.9% ENTRESTO

In the double-blind period, incidence of angioedema with ENTRESTO was 0.5% vs 0.2% with enalapril:

- Incidence of angioedema in Black patients treated with ENTRESTO was 2.4% vs 0.5% with enalapril
- No incidence of angioedema was associated with airway compromise

*Data reflect double-blind period only.
1 Due to the run-in period, adverse event rates were lower than would be expected in practice.
2 0.5% vs 0.7% discontinued due to hypotension in the ENTRESTO arm and enalapril arm, respectively.
3 Median duration of exposure during the run-in period was 15 days for enalapril and 29 days for ENTRESTO.
Start ENTRESTO with confidence

76% OF PATIENTS IN THE TITRATION STUDY ACHIEVED AND MAINTAINED THE TARGET DOSE OF ENTRESTO WITHOUT INTERRUPTION OR ADJUSTMENT*

TITRATION Study

- TITRATION was a 12-week tolerability study in 498 patients with HF/EF who were either naïve to or on varying doses of ACEi or ARB therapy prior to study entry
- The primary objective was to characterize the safety and tolerability of both a 3-week and 6-week ENTRESTO up-titration regimens
- After a 1-week run-in phase where all subjects received ENTRESTO 24/26 mg twice a day, patients were randomized to continue with either a 3-week condensed regimen or a 6-week conservative regimen. (After patients were initiated on ENTRESTO 24/26 mg twice daily, they were then up-titrated to 49/51 mg twice daily, and then up-titrated again to the target dose of 97/103 mg twice daily.)

*Among all randomized patients who received at least 1 dose of study medication and excluding those who discontinued due to reasons not related to adverse events or death.9

IMPORTANT SAFETY INFORMATION, CONT’D

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%).

ENTRESTO is available in 3 dosage strengths1

The target dose for ENTRESTO is 97/103 mg twice daily

The starting dose of ENTRESTO is 24/26 mg twice daily or 49/51 mg twice daily, depending on a patient’s current treatment*

- Dosing in clinical trials was based on the total amount of both components of ENTRESTO (ie, 24/26 mg, 49/51 mg, and 97/103 mg were referred to as 50 mg, 100 mg, and 200 mg, respectively)

ENTRESTO may be administered with or without food.

Visit EntrestoHCP.com/dosing for an interactive guide on administering ENTRESTO

*ENTRESTO is contraindicated with concomitant use of an ACEi. If switching from an ACEi to ENTRESTO, allow a washout period of 36 hours between administration of the two drugs. Avoid use of ENTRESTO with an ARB, because ENTRESTO contains the ARB valsartan.1

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REDEFINE EXPECTATIONS IN HEART FAILURE

EntrestoHCP.com


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