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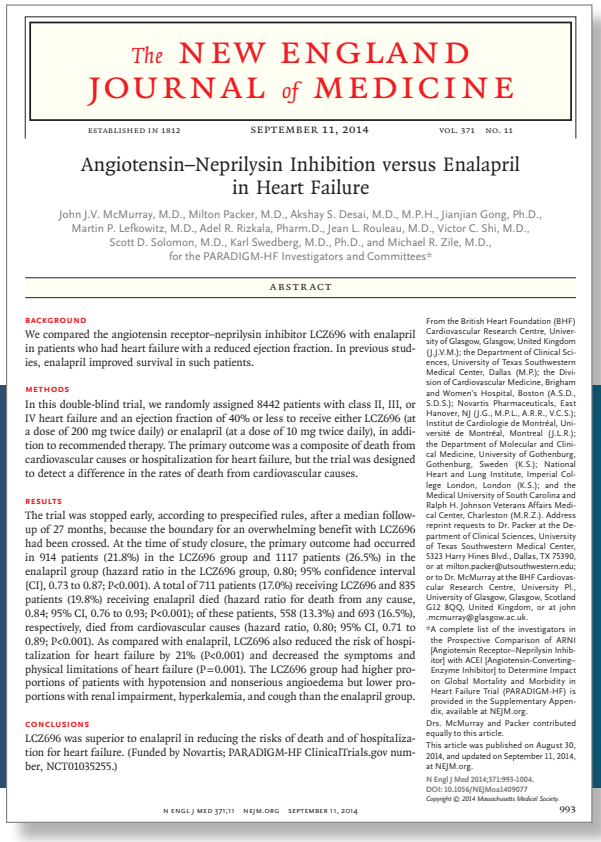
# PARADIGM-HF trial:*

## PrENTRESTO® compared to enalapril in patients with HFrEF and symptomatic CHF[1,2]



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Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

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ABSTRACT

BACKGROUND
We compared the angiotensin receptor–neprilysin inhibitor LCZ696 with enalapril in patients who had heart failure with a reduced ejection fraction. In previous studies, enalapril improved survival in such patients.

METHODS
In this double-blind trial, we randomly assigned 8442 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either LCZ696 (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to recommended therapy. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure, but the trial was designed to detect a difference in the rates of death from cardiovascular causes.

RESULTS
The trial was stopped early, according to prespecified rules, after a median follow-up of 27 months, because the boundary for an overwhelming benefit with LCZ696 had been crossed. At the time of study closure, the primary outcome had occurred in 914 patients (21.8%) in the LCZ696 group and 1117 patients (26.5%) in the enalapril group (hazard ratio in the LCZ696 group, 0.80; 95% confidence interval [CI], 0.73 to 0.87; P<0.001). A total of 711 patients (17.0%) receiving LCZ696 and 835 patients (19.8%) receiving enalapril died (hazard ratio for death from any cause, 0.84; 95% CI, 0.76 to 0.93; P<0.001); of these patients, 558 (13.3%) and 693 (16.5%), respectively, died from cardiovascular causes (hazard ratio, 0.80; 95% CI, 0.71 to 0.89; P<0.001). As compared with enalapril, LCZ696 also reduced the risk of hospitalization for heart failure by 21% (P<0.001) and decreased the symptoms and physical limitations of heart failure (P=0.001). The LCZ696 group had higher proportions of patients with hypotension and nonserious angioedema but lower proportions with renal impairment, hyperkalemia, and cough than the enalapril group.

CONCLUSIONS
LCZ696 was superior to enalapril in reducing the risks of death and of hospitalization for heart failure. (Funded by Novartis; PARADIGM-HF ClinicalTrials.gov number, NCT01035255.)

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*A complete list of the investigators in the Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] with ACEI [Angiotensin-Converting–Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF) is provided in the Supplementary Appendix, available at NEJM.org.

Drs. McMurray and Packer contributed equally to this article.

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***"The primary objective of PARADIGM-HF was to determine whether ENTRESTO®, a combination of sacubitril and valsartan, was superior to enalapril alone in reducing the risk of the combined endpoint of cardiovascular (CV) death or hospitalization for heart failure (HF)."***[1]

ENTRESTO® (sacubitril/valsartan) is indicated for the treatment of heart failure with reduced ejection fraction (HFrEF) in patients with NYHA Class II or III, to reduce the incidence of cardiovascular (CV) death and heart failure (HF) hospitalization.[1]

ENTRESTO® should be administered in combination with other heart failure therapies, in place of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB).

* **P**rospective Comparison of **ARNI** [Angiotensin Receptor-Neprilysin Inhibitor] with **A**CEi [Angiotensin-Converting Enzyme Inhibitor] to **D**etermine **I**mpact on **G**lobal **M**ortality and Morbidity in **H**eart **F**ailure Trial.
CHF = chronic heart failure; HFrEF = heart failure with reduced ejection fraction.

Pr Entresto®
sacubitril/valsartan

# PARADIGM-HF trial:†

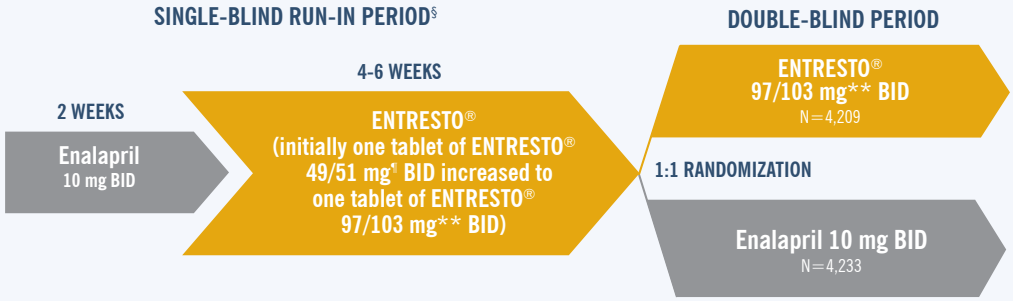
**PARADIGM-HF TRIAL:**
The largest published clinical trial in heart failure[3]*

- The primary endpoint was the first event in the composite of CV death or hospitalization for HF

## Trial design[1,2]

- PARADIGM-HF was a multinational, randomized, double-blind trial conducted in over 8,400 patients with symptomatic chronic HF and reduced ejection (LVEF ≤40% in NYHA Class II-IV‡)

After discontinuing their existing ACEi or ARB therapy, patients entered sequential single-blind run-in periods




BID=twice daily.

Adapted from the ENTRESTO® Product Monograph and McMurray *et al.*[1,2]

- At randomization, **70% of patients were NYHA Class II, 24% NYHA Class III, and 0.7% NYHA Class IV** (ENTRESTO® is only indicated in NYHA Class II and III). **Patients were also taking beta-blockers (94%), mineralocorticoid antagonists (58%), and diuretics (82%).**
- The median follow-up duration of double-blind treatment was 27 months, with some patients treated for up to 4.3 years.[1,2]

## Selected baseline characteristics[2]

| Characteristics | | ENTRESTO® (N=4,187) | Enalapril (N=4,212) |
|---|---|---|---|
| Age | | 63.8 years | 63.8 years |
| Gender | Male | 3,308 (79.0%) | 3,259 (77.4%) |
| | Female | 879 (21.0%) | 953 (22.6%) |
| Systolic blood pressure | | 122 mmHg | 121 mmHg |
| Serum creatinine | | 1.13 mg/dl | 1.12 mg/dl |
| Ischemic cardiomyopathy†† | | 2,506 (59.9%) | 2,530 (60.1%) |
| Left ventricular ejection fraction | | 29.6% | 29.4% |
| Median NT-proBNP‡‡ | | 1,631 pg/ml | 1,594 pg/ml |

| Characteristics | | ENTRESTO® (N=4,187) | Enalapril (N=4,212) |
|---|---|---|---|
| NYHA class§§ | I | 180 (4.3%) | 209 (5.0%) |
| | II | 2,998 (71.6%) | 2,921 (69.3%) |
| | III | 969 (23.1%) | 1,049 (24.9%) |
| | IV | 33 (0.8%) | 27 (0.6%) |
| | Missing data | 7 (0.2%) | 6 (0.1%) |
| Medical history | Hypertension | 2,969 (70.9%) | 2,971 (70.5%) |
| | Diabetes | 1,451 (34.7%) | 1,456 (34.6%) |
| | Atrial fibrillation | 1,517 (36.2%) | 1,574 (37.4%) |
| | Hospitalization for heart failure | 2,607 (62.3%) | 2,667 (63.3%) |
| | Myocardial infarction | 1,818 (43.4%) | 1,816 (43.1%) |
| | Stroke | 355 (8.5%) | 370 (8.8%) |
| | Pretrial use of ACEi¶¶ | 3,266 (78.0%) | 3,266 (77.5%) |
| | Pretrial use of ARB¶¶ | 929 (22.2%) | 963 (22.9%) |

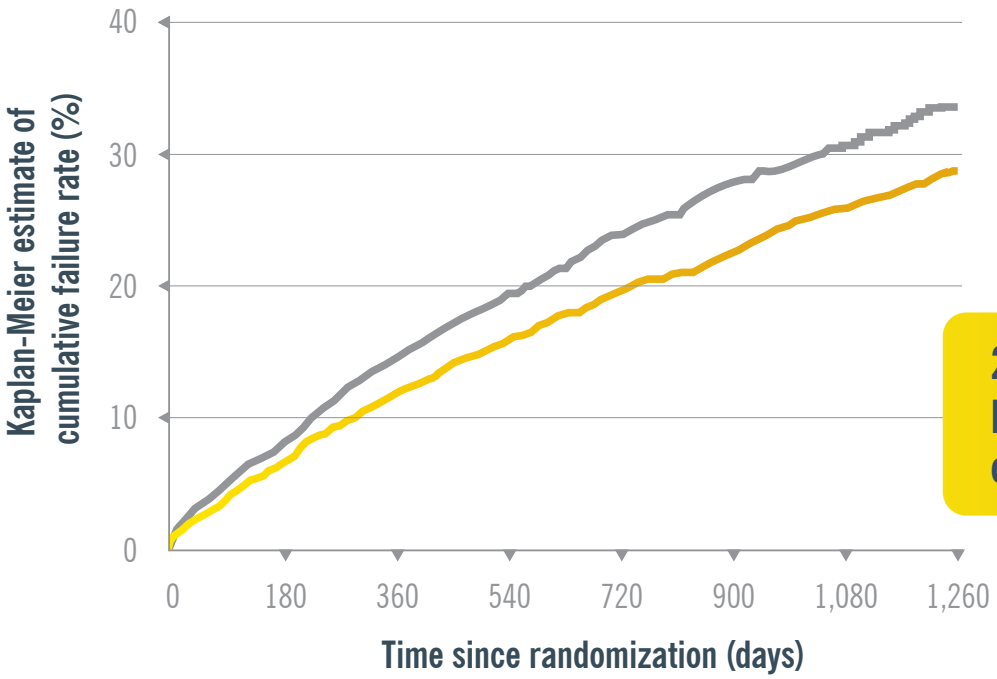
* Comparative clinical significance is unknown.
† **P**rospective Comparison of **AR**NI [Angiotensin Receptor-Neprilysin Inhibitor] with **A**CEI [Angiotensin-Converting Enzyme Inhibitor] to **D**etermine **I**mpact on **G**lobal **M**ortality and Morbidity in **H**eart **F**ailure Trial.
‡ ENTRESTO® is only indicated in NYHA Class II and III.
§ Essentially all patients were taking an ACEi or ARB prior to run-in period.
¶ ENTRESTO® 49 mg sacubitril/51 mg valsartan containing 48.6 mg sacubitril and 51.4 valsartan as sacubitril valsartan sodium hydrate complex (referred to as 100 mg in the Clinical Trial).
** ENTRESTO® 97 mg sacubitril/103 mg valsartan containing 97.2 mg sacubitril and 102.8 valsartan as sacubitril valsartan sodium hydrate complex (referred to as 200 mg in the Clinical Trial).
†† ENTRESTO® should not be initiated in patients with acutely decompensated HF, or clinically relevant ischemic events, such as acute myocardial or cerebral infarction.
‡‡ Due to the action of sacubitril on BNP levels, only NT-proBNP may be a suitable biomarker for the monitoring of heart failure patients treated with ENTRESTO®.
§§ The data for NYHA class reflect the status of patients at the time of randomization. Patients were required to have at least NYHA class II symptoms at screening.
¶¶ At the screening visit, 20 patients were not receiving the protocol-required treatment with ACEi or an ARB, and 45 patients were taking both drugs.
NT-proBNP=N-terminal pro–B-type natriuretic peptide; NYHA=New York Heart Association.

# In PARADIGM-HF, ENTRESTO® demonstrated 20% reduced instantaneous risk of combined CV death or first HF hospitalization vs. enalapril

**(HR: 0.80 [95% CI: 0.73-0.87]; 1-sided $p=0.0000002$) (primary endpoint)[1,2*†]**

## Clinically relevant and statistically significant superiority to enalapril was shown for combined CV death or first HF hospitalization in patients with HF with reduced ejection fraction[1,2]

### Time to first occurrence of CV death or HF hospitalizations in PARADIGM-HF




**Enalapril**
(N=4,212)

**ENTRESTO®**
(N=4,187)

$p=0.0000002$
HR (95% CI): 0.80
(0.73-0.87)

**21 patients would need to have been treated (NNT) to prevent one primary event**

| No. at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| ENTRESTO® | 4,187 | 3,922 | 3,663 | 3,018 | 2,257 | 1,544 | 896 | 249 |
| Enalapril | 4,212 | 3,883 | 3,579 | 2,922 | 2,123 | 1,488 | 853 | 236 |

Adapted from the ENTRESTO® Product Monograph and McMurray *et al.*[1,2]

*The PARADIGM-HF trial was a multinational, randomized, double-blind trial comparing ENTRESTO® (sacubitril/valsartan) to enalapril in 8,442 adult patients with symptomatic chronic heart failure and reduced ejection, i.e., left ventricular ejection fraction ≤40% in NYHA Class II-IV. Prior to study enrollment, patients were required to have a plasma B-type natriuretic peptide (BNP) ≥150 pg/mL or N-terminal pro-BNP (NT-proBNP) ≥600 pg/mL, or, if they had been hospitalized for heart failure in the last 12 months, a BNP ≥100 pg/mL or a NT-proBNP ≥400 pg/mL. Patients had to have been on an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) at a dose equivalent to at least 10 mg of enalapril daily for at least four weeks prior to screening, and on maximally tolerated doses of beta-blockers. After discontinuing their existing ACEi or ARB therapy, patients entered sequential single-blind run-in periods during which they received enalapril 10 mg twice daily for a median duration of 15 days, followed by one tablet of ENTRESTO® 49 mg sacubitril/51 mg valsartan containing 48.6 mg sacubitril and 51.4 valsartan as sacubitril valsartan sodium hydrate complex (referred to as 100 mg in the Clinical Trial) taken twice daily, for a median duration of 29 days. Patients who successfully completed the sequential run-in periods were randomized to receive either one tablet of ENTRESTO® 97 mg sacubitril/103 mg valsartan containing 97.2 mg sacubitril and 102.8 valsartan as sacubitril valsartan sodium hydrate complex (referred to as 200 mg in the Clinical Trial) (N=4,209) twice daily or enalapril 10 mg (N=4,233) twice daily in a double-blind manner. At randomization, 70% were NYHA Class II, 24% NYHA Class III, and 0.7% NYHA Class IV (ENTRESTO® is only indicated in NYHA Class II and III). Patients were also taking beta-blockers (94%), mineralocorticoid antagonists (58%), and diuretics (82%). The primary endpoint was the first event in the composite of CV death or hospitalization for HF. The median follow-up duration of double-blind treatment was 27 months, with some patients treated for up to 4.3 years.

†ARR=4.7%

# Summary of PARADIGM-HF efficacy results

Component of **primary endpoint**

**First HF hospitalization**

21% RR
HR: 0.79 (95% CI: 0.71-0.89)
$p=0.00004^{\ddagger}$

ENTRESTO® 537/4,187
Enalapril 658/4,212

**Primary endpoint**

Primary composite of
**First HF hospitalization and CV death***

20% RR
HR: 0.80 (95% CI: 0.73-0.87)
$p=0.0000002^{\ddagger}$

ENTRESTO® 914/4,187
Enalapril 1,117/4,212

Component of **primary endpoint**

**CV death**†

20% RR
HR: 0.80 (95% CI: 0.71-0.89)
$p=0.00004^{\ddagger}$

ENTRESTO® 558/4,187
Enalapril 693/4,212

## Secondary endpoints

**Total HF hospitalization**

ENTRESTO® 851/4,187
Enalapril 1,079/4,212

23% RR
HR: 0.77 (95% CI: 0.67-0.89)
$p=0.00004^{\ddagger}$

**Sudden death** (accounted for 45% of CV deaths)

ENTRESTO® 250/4,187
Enalapril 311/4,212

20% RR
HR: 0.80 (95% CI: 0.68-0.94)
$p=0.008^{\ddagger}$

**All-cause mortality**

ENTRESTO® 711/4,187
Enalapril 835/4,212

16% RR
HR: 0.84 (95% CI: 0.76-0.93)
$p=0.0005^{\ddagger}$

Adapted from the ENTRESTO® Product Monograph, Packer *et al.* and Desai *et al.*[1,4,5]

## In PARADIGM-HF, risk reduction with ENTRESTO® (composite of first HF hospitalization and CV death) was consistent across subgroups, including:[1,2]

- Age
- Gender
- Race
- Geography

- Ejection fraction
- Renal function
- History of hypertension
- History of diabetes
- Presence of atrial fibrillation

# ENTRESTO®: A proven safety and tolerability profile in PARADIGM-HF[1]

Because of the run-in design of the PARADIGM-HF trial, the adverse reaction rates in the randomized double-blind period of the trial may be lower than those expected to be seen in actual clinical practice.*

## Summary of adverse events of interest occurring in ≥5% of patients in the randomized, double-blind phase of PARADIGM-HF[1]

| ADVERSE EVENTS | ENTRESTO®§ N=4,203 (%) | Enalapril¶ N=4,229 (%) |
|---|---|---|
| Hypotension | 17.6 | 12.0 |
| Hyperkalemia | 11.6 | 14.0 |
| Renal impairment | 10.1 | 11.5 |
| Cough | 8.8 | 12.6 |
| Dizziness | 6.3 | 4.9 |
| Renal failure, including acute | 4.9 | 5.6 |

§ ENTRESTO® dosed up to 97.2 mg sacubitril/102.8 mg valsartan BID.
¶ Enalapril dosed up to 10 mg BID.

Adapted from the ENTRESTO® Product Monograph[1]

**Discontinuation of therapy** due to an adverse event in the double-blind period of the PARADIGM-HF trial **occurred in 10.7% of ENTRESTO®-treated patients vs. 12.2% of enalapril-treated patients**[1††]

ENTRESTO®-treated patients who experienced a hypotensive event in the double-blind treatment phase were more commonly observed to have other associated hypotensive adverse events, compared to enalapril-treated patients, such as post-baseline systolic blood pressure (SBP) <90 mmHg (5.2% vs. 3.1%, respectively), a drop ≥30 mmHg in SBP from baseline (5.4% vs. 3.2%), and simultaneous symptomatic hypotension and SBP <90 mmHg (2.8% vs. 1.5%).

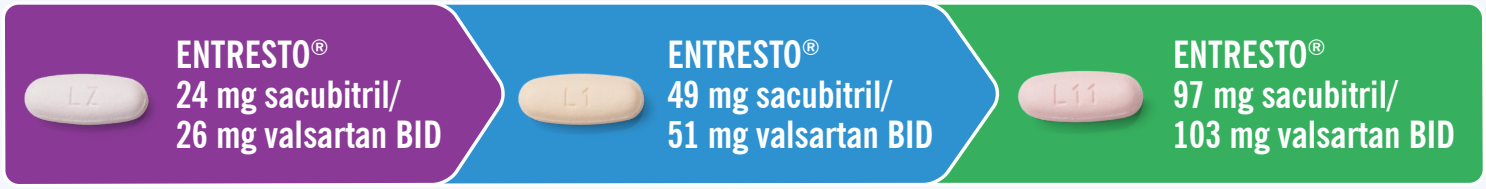
* The primary endpoint was defined as the time-to-first-event.
† CV death includes all patients who died up to the cut-off date irrespective of previous hospitalization.
‡ Two-sided *p*-value for Total HF hospitalizations, all other *p*-values one-sided as pre-specified.
†† In the PARADIGM-HF trial, patients were required to complete sequential single-blind enalapril and ENTRESTO® run-in periods of a median duration of 15 and 29 days, respectively, prior to entering the randomized double-blind period, comparing ENTRESTO® and enalapril. During the enalapril run-in period, 1,102 patients (10.5%) were permanently discontinued from the study, 5.6% because of an adverse event, most commonly renal dysfunction (1.7%), hyperkalemia (1.7%) and hypotension (1.4%). During the ENTRESTO® run-in period, which followed the enalapril run-in phase, an additional 10.4% of patients permanently discontinued treatment, 5.9% because of an adverse event, most commonly renal dysfunction (1.8%), hypotension (1.7%) and hyperkalemia (1.3%).

# Initiating and titrating ENTRESTO® to target dose[1]

ENTRESTO® should only be initiated in clinically stable patients whose baseline systolic blood pressure, serum potassium and renal function are at acceptable levels.

**Patients with:**
- ACEi or ARB at less than guideline-recommended doses
- Risk for hypotension (≥75 years old, low SBP)
- Moderate hepatic impairment (Child-Pugh B)

**Starting dose** → **Target dose**




After 2-4 weeks as tolerated by patient — After 2-4 weeks as tolerated by patient

**Patients with:**
- Prior ACEi or ARB at guideline-recommended doses

**Starting dose** → **Target dose**


After 2-4 weeks as tolerated by patient

SBP = systolic blood pressure.

Adapted from the ENTRESTO® Product Monograph[1]

If patients experience tolerability issues, e.g., symptomatic hypotension or hyperkalemia, consideration should be given to temporary down-titration or treatment interruption of ENTRESTO®.

ENTRESTO® should normally be used in conjunction with other medical treatment for HF, including diuretics, beta-blockers, and mineralocorticoid receptor antagonists, as appropriate and as tolerated.

Administer ENTRESTO® with or without food.

### Stop ACEi therapy for a 36-hour washout

- ENTRESTO® must **not** be started until at least **36 hours have passed following discontinuation of ACEi therapy**[1]
- **Example:** If a patient's last dose of ACEi was on Friday evening, then he/she can start ENTRESTO® on Monday morning

**ENTRESTO® must not be administered with any drug formulation containing an ACEi due to the risk of angioedema and should not be administered with any other drug formulation containing an ARB[1]**

**Clinical use not discussed elsewhere in this piece:**

ENTRESTO® should be initiated, and up-titration conducted, by a physician experienced with the treatment of heart failure.

No dosage adjustment is required in patients over 65 years. However, ENTRESTO® has been studied in a limited number of patients above the age of 80 years. Caution is required in these patients.

The safety and efficacy of ENTRESTO® in pediatric patients (<18 years of age) has not been established.

**Contraindications:**

- Recent symptomatic hypotension prior to initiation of treatment with ENTRESTO® (sacubitril/valsartan)
- Concomitant use with any drug formulation containing an ACEi, due to potential enhanced risk of angioedema. **ENTRESTO® must not be administered until at least 36 hours have elapsed following discontinuation of ACEi therapy.**
- Known history of angioedema related to previous ACEi or ARB therapy
- History of hereditary or idiopathic angioedema
- As for any formulation containing an ACEi or ARB, use of ENTRESTO® together with aliskiren-containing drugs is contraindicated in patients with diabetes mellitus, whether Type 1 or 2, or in patients with moderate to severe renal impairment, i.e., eGFR <60 mL/min/1.73 $m^2$.
- Pregnant and nursing women
- Hypersensitivity to the active substances, sacubitril or valsartan, or to any of the excipients

**Most serious warnings and precautions:**

**Use in pregnancy:** When used in pregnancy, ARBs can cause injury to or even death of the developing fetus. When pregnancy is detected, ENTRESTO® should be discontinued as soon as possible.

**Use of ACEi:** ENTRESTO® must not be initiated until at least 36 hours have elapsed following discontinuation of ACEi therapy due to the risk of angioedema. If treatment with ENTRESTO® is stopped, ACEi therapy must not be initiated until 36 hours after the last dose of ENTRESTO®.

**NT-proBNP monitoring:** Due to the action of sacubitril on BNP levels, only NT-proBNP may be a suitable biomarker for the monitoring of heart failure patients treated with ENTRESTO®.

**Use of medications known to raise serum potassium levels:** Caution should be exercised when co-administering ENTRESTO® with medications known to raise serum potassium levels (e.g., potassium-sparing diuretics, potassium supplements).

**Other relevant warnings and precautions:**

- ENTRESTO® should not be administered with any other drug formulation containing an ARB.
- Caution when co-administering ENTRESTO® with direct renin inhibitors such as aliskiren.
- Angioedema: Caution is recommended in patients with a prior history of any angioedema and in Black patients.
- Symptomatic hypotension: ENTRESTO® is not recommended in patients with systolic blood pressure <100 mmHg at the time of treatment initiation.
- Hyperkalemia: Measure serum potassium before instituting ENTRESTO®, and during treatment, as appropriate, taking into account the patient's predisposition to develop hyperkalemia. Patients with serum potassium >5.2 mmol/L prior to initiation of treatment with ENTRESTO® have not been studied. Careful monitoring of serum potassium is recommended in patients with severe renal impairment, diabetes mellitus, hypoaldosteronism, or a high potassium intake in their diet.
- Decreases in renal function in susceptible individuals. Closely monitor serum creatinine, and down-titrate or interrupt ENTRESTO® in patients who develop a clinically significant decrease in renal function. Before initiation of therapy and during treatment, assess renal function, as appropriate.
- Caution in patients with renal artery stenosis, if ENTRESTO® is to be used. Careful monitoring of renal function should be carried out.
- Advising women of child-bearing potential to use contraception during treatment with ENTRESTO® and for one (1) week after their last dose.
- Nursing women: Because of the potential risk for adverse drug reactions in breastfed newborns, a decision should be made whether to abstain from breast-feeding or to discontinue ENTRESTO® while breast-feeding, taking into account the importance of ENTRESTO® to the mother.
- A starting dose of 24 mg sacubitril/26 mg valsartan twice daily is recommended in patients with moderate hepatic impairment (Child-Pugh B). ENTRESTO® is not recommended in patients with severe hepatic impairment (Child-Pugh C).
- ENTRESTO® is not recommended in patients with severe renal impairment (eGFR <30 mL/min/1.73 $m^2$).

**For more information:**

Please consult the Product Monograph at www.novartis.ca/EntrestoMonograph for important information relating to adverse reactions, drug interactions, and dosing information which have not been discussed in this piece. The Product Monograph is also available by calling 1-800-363-8883 or via medinfo.canada@novartis.com.

**References: 1.** ENTRESTO® Product Monograph. Novartis Pharmaceuticals Canada Inc. July 13, 2021. **2.** McMurray JJ, Packer M, Desai AS *et al*. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;371:993-1004. **3.** Novartis Data on File – PARADIGM. 2020. **4.** Desai AS, McMurray JJ, Packer M *et al*. Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients. *Eur Heart J* 2015;36(30):1990-7. **5.** Packer M, McMurray JJ, Desai AS *et al*. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. *Circulation* 2015;131:54-61. **6.** McDonald M, Virani S, Chan M *et al.* CCS/CHFS Heart Failure Guidelines Update: Defining a New Pharmacologic Standard of Care for Heart Failure With Reduced Ejection Fraction. *Can J Cardiol* 2021;37(4):531-546.

## When your patients have

**An Ejection Fraction ≤40%** & **NYHA Class II or III Symptoms**

# CONSIDER ENTRESTO®

**To reduce the incidence of heart failure hospitalization and CV death**[1]

## ENTRESTO® demonstrated a 20% reduced risk of combined CV death or first HF hospitalization* vs. enalapril (HR: 0.80 [95% CI: 0.73-0.87]; 1-sided $p=0.0000002$)[1,2]

Incidence of events, n (%): 914 (21.8%) vs. 1,117 (26.5%)

## ENTRESTO® tablets available in 3 doses:†


## Recommended as a standard therapy for HFrEF:[6‡]

## The 2021 CCS HF Guidelines recommend ARNI as a standard therapy for HFrEF, in combination with other standard therapies

* The primary endpoint was defined as the time-to-first-event.
† Clinical significance unknown.
‡ Please consult guidelines for complete recommendations.
ARNI = angiotensin receptor-neprilysin inhibitor; GDMT = guideline-directed medical therapy.

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