PrENTRESTO®:

HFrEF patient case studies*

Tony
64 years old

Jeremy
70 years old

Frances
72 years old

Louise
68 years old

George
58 years old

Edwin
74 years old

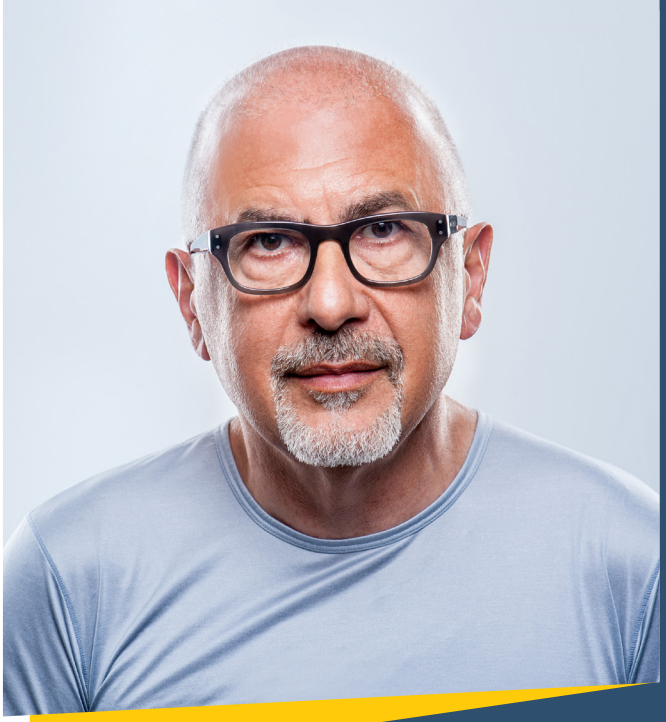
Consider ENTRESTO® in these patients.

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).

* Fictitious patient cases. May not be representative of all patients.[1-3]
HFrEF = heart failure with reduced ejection fraction, NYHA = New York Heart Association.

PrEntresto®
sacubitril/valsartan



Meet Tony*

Profile

- 64-year-old man
- Retired truck driver
- Current smoker
- HFrEF diagnosed 1 year ago
- **Comorbidities/medical history:**
  - Myocardial infarction 18 months ago
  - Low normal blood pressure

Would you consider ENTRESTO® for Tony?

Current Presentation

- Tony reports that over the past few months he has been experiencing:
  - Shortness of breath
    - Worsens with exertion (e.g., going up and down the stairs)
  - Fatigue
  - Occasional episodes of palpitations
- Clinical parameters:
  - LVEF: 30%
  - BP: 110/75 mmHg
  - Heart rate: 65 bpm

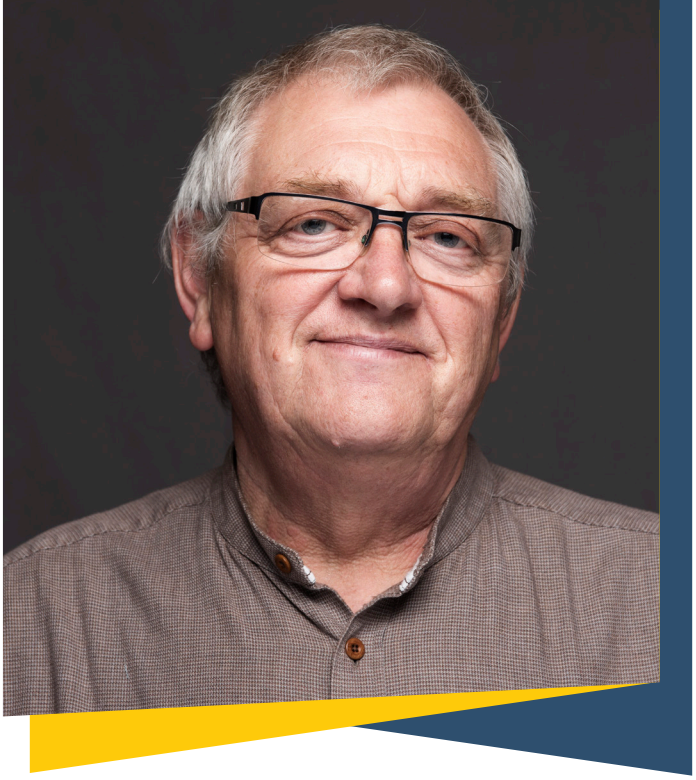
Current Medications[4-7]

- Ramipril 2.5 mg BID†
- Metoprolol 100 mg BID
- Eplerenone 50 mg QD
- Acetylsalicylic acid 81 mg QD

* Fictitious patient case. May not be representative of all patients.[1-3]

† Concomitant use with any drug formulation containing an ACEi is contraindicated. ENTRESTO® must not be administered until at least 36 hours have elapsed following discontinuation of ACEi therapy.

BP=blood pressure; LVEF=left ventricle ejection fraction.



Meet Jeremy*

Profile

- 70-year-old man
- Retired principal
- **Comorbidities/medical history:**
  - Obesity
  - Type 2 diabetes
  - Mild renal impairment

Would you consider ENTRESTO® for Jeremy?

Current Presentation

- Jeremy reports the following symptoms:
  - Shortness of breath (especially while lying down)
  - Fatigue
  - Palpitations
- Clinical parameters:
  - LVEF: 26%
  - BP: 115/75 mmHg
  - Heart rate: 84 bpm
  - eGFR: 63.4 mL/min/1.73m^2
  - Latest HbA1c: 7.4%
  - BMI: 33.5 kg/m^2

Current Medications[8-10]

- Perindopril 4 mg QD†
- Furosemide 40 mg QD‡
- Metformin (extended release) 1000 mg QD‡

* Fictitious patient case. May not be representative of all patients.[1-3]

† Concomitant use with any drug formulation containing an ACEi is contraindicated. ENTRESTO® must not be administered until at least 36 hours have elapsed following discontinuation of ACEi therapy.

‡ Furosemide and metformin may interact with ENTRESTO®.

BMI=body-mass index; BP=blood pressure; eGFR=estimated glomerular filtration rate; LVEF=left ventricle ejection fraction.

Pr Entresto®
sacubitril/valsartan

Meet Frances*

Profile

- 72-year-old woman
- Retired nurse
- **Comorbidities/medical history:**
  - Atrial fibrillation
  - Hypertension
  - Obesity
  - Mild hepatic impairment

Would you consider ENTRESTO® for Frances?

Current Presentation

- Frances often feels short of breath and anginal pain when running errands
- Clinical parameters:
  - LVEF: 29%
  - BP: 137/85 mmHg
  - Heart rate: 80 bpm
  - BMI: 31.4 kg/m^2

Current Medications[6,11,12]

- Valsartan 160 mg BID†
- Bisoprolol 10 mg QD
- Eplerenone 50 mg QD

* Fictitious patient case. May not be representative of all patients.[1-3]
† ENTRESTO® should not be administered with any other drug formulation containing an ARB, due to the angiotensin II receptor blocking activity of ENTRESTO®.
BMI=body-mass index; BP=blood pressure; LVEF=left ventricle ejection fraction.

Meet Louise*

Profile

- 68-year-old woman
- Retired retail worker
- Former smoker
- **Comorbidities/medical history:**
  - Type 2 diabetes
  - Overweight
  - Low normal blood pressure

Would you consider ENTRESTO® for Louise?

Current Presentation

- Louise has been experiencing palpitations when she goes on her hikes
- Clinical parameters:
  - LVEF: 32%
  - BP: 108/77 mmHg
  - Heart rate: 62 bpm
  - Latest HbA1c: 6.8%
  - BMI: 28.5 kg/m^2

Current Medications[4,10]

- Ramipril 5 mg QD†
- Metformin (extended release) 1000 mg QD‡

* Fictitious patient case. May not be representative of all patients.[1-3]
† Concomitant use with any drug formulation containing an ACEi is contraindicated. ENTRESTO® must not be administered until at least 36 hours have elapsed following discontinuation of ACEi therapy.
‡ Metformin may interact with ENTRESTO®.
BMI=body-mass index; BP=blood pressure; LVEF=left ventricle ejection fraction.

Pr Entresto®
sacubitril/valsartan

Meet George*

Profile

- 58-year-old man
- Insurance broker
- **Comorbidities/medical history:**
  - Moderate renal impairment
  - Hypertension

Would you consider ENTRESTO® for George?

Current Presentation

- George reports that he often experiences fatigue and breathlessness on his walks to and from work
- Clinical parameters:
  - LVEF: 34%
  - BP: 133/82 mmHg
  - Heart rate: 83 bpm
  - eGFR: 42.0 mL/min/1.73m^2

Current Medications[4,5,9]

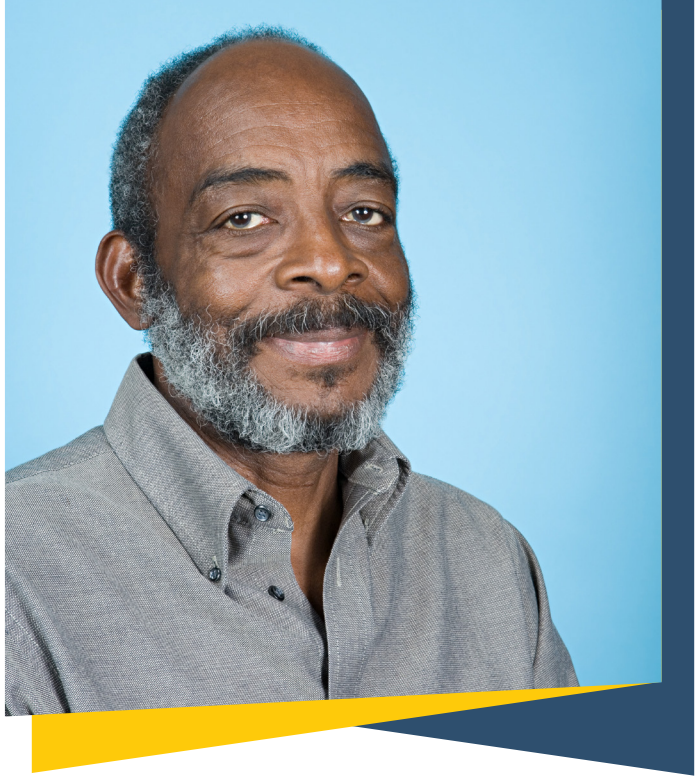
- Ramipril 1.25 mg BID†
- Metoprolol 100 mg BID
- Furosemide 20 mg QD‡

* Fictitious patient case. May not be representative of all patients.[1-3]

† Concomitant use with any drug formulation containing an ACEi is contraindicated. ENTRESTO® must not be administered until at least 36 hours have elapsed following discontinuation of ACEi therapy.

‡ Furosemide may interact with ENTRESTO®.

BP=blood pressure; eGFR=estimated glomerular filtration rate; LVEF=left ventricle ejection fraction.



Meet Edwin*

Profile

- 74-year-old man
- Former smoker
- Retired chef
- **Comorbidities/medical history:**
  - Type 2 diabetes
  - Hypertension

Would you consider ENTRESTO® for Edwin?

Current Presentation

- During a regular checkup: reports having difficulty going on his weekend walks with his granddaughter since he started experiencing pains in his chest
- Clinical parameters:
  - LVEF: 31%
  - BP: 136/84 mmHg
  - Heart rate: 77 bpm
  - Latest HbA1c: 6.5%

Current Medications[4,5,10,13,14]

- Ramipril 10 mg QD†
- Atorvastatin 10 mg QD‡
- Metoprolol 100 mg BID
- Metformin (extended release) 1000 mg QD§
- Dapagliflozin 10 mg QD

* Fictitious patient case. May not be representative of all patients.[1-3]
† Concomitant use with any drug formulation containing an ACEi is contraindicated. ENTRESTO® must not be administered until at least 36 hours have elapsed following discontinuation of ACEi therapy.
‡ Caution should be exercised upon co-administration of ENTRESTO® with statins.
§ Metformin may interact with ENTRESTO®.
BP=blood pressure; LVEF=left ventricle ejection fraction.

Pr Entresto®
sacubitril/valsartan

PARADIGM-HF TRIAL:
The largest published clinical trial in heart failure[2,15]*

Act with ENTRESTO® to reduce the risk of CV death and first HF hospitalization[1,2]

Primary composite of

First HF hospitalization and CV death†

ENTRESTO® 914/4,187
Enalapril 1,117/4,212
21.8% vs. 26.5%

20% RR

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

This effect was observed early and was sustained throughout the trial[1]

* Comparative clinical significance is unknown. See references for study design.[2]
† The primary endpoint was defined as the time-to-first-event.
‡ Two-sided p-value for Total HF hospitalizations, all other p-values one-sided as pre-specified.
§ Fictitious patient case. May not be representative of all patients.
CV=cardiovascular; HF=heart failure; RR=risk reduction.

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

Secondary endpoints[1]

Total HF hospitalization

23% RR

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

ENTRESTO® 851/4,187
Enalapril 1,079/4,212
20.3% vs. 25.6%

Sudden death (accounted for 45% of CV deaths)

20% RR

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

ENTRESTO® 250/4,187
Enalapril 311/4,212
6.0% vs. 7.4%

All-cause mortality

16% RR

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

ENTRESTO® 711/4,187
Enalapril 835/4,212
17.0% vs. 19.8%

Pr Entresto®
sacubitril/valsartan

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:
- Prior ACE inhibitor 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**

ENTRESTO® 24 mg sacubitril/ 26 mg valsartan BID	ENTRESTO® 49 mg sacubitril/ 51 mg valsartan BID	ENTRESTO® 97 mg sacubitril/ 103 mg valsartan BID
	After 2-4 weeks as tolerated by patient	After 2-4 weeks as tolerated by patient

Patients with:
- Prior ACE inhibitor or ARB at guideline-recommended doses

Starting dose → **Target dose**

ENTRESTO® 49 mg sacubitril/ 51 mg valsartan BID	ENTRESTO® 97 mg sacubitril/ 103 mg valsartan BID
	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®.[1]

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.[1]

ENTRESTO® must not be administered with any drug formulation containing an ACE inhibitor due to the risk of angioedema and should not be co-administered with any other drug formulation containing an ARB.[1]

Stop ACE inhibitor therapy for a 36-hour washout.[1]

ENTRESTO® must **not** be started until **36 hours have passed following discontinuation of ACE inhibitor therapy.**[1]

ENTRESTO® should be used in place of an ACE inhibitor or ARB.[1]

Clinical use:

- ENTRESTO® should be administered in combination with other heart failure therapies, in place of an ACEi or ARB.
- 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 of ARB 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 administered with an ACEi due to the risk of angioedema.

Use of ARB: ENTRESTO® should not be administered with any other drug formulation containing an ARB, due to the angiotensin II receptor blocking activity of ENTRESTO® by its valsartan moiety.

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 co-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, ENTRESTO® is not recommended during breastfeeding.
- 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. The PARADIGM-HF trial was a multinational, randomized, double-blind trial comparing ENTRESTO® (sacubitril/valsartan) to enalapril in 8,442 adult patients with HFrEF. Patients were randomized to receive either ENTRESTO® 200 mg (97.2 mg sacubitril and 102.8 valsartan; N=4,209) twice daily or enalapril 10 mg twice daily (N=4,233) in addition to recommended therapy. The primary endpoint was the first event in the composite of CV death or hospitalization for HF. **3.** American Heart Association. Classification of Functional Capacity and Objective Assessment. Available at: https://professional.heart.org/en/guidelines-and-statements/classification **4.** ALTACE® (ramipril) Product Monograph. Bausch Health, Canada Inc. January 8, 2021. **5.** APO-METOPROLOL (metoprolol) Product Monograph. Apotex Inc. January 13, 2021. **6.** MINT-EPLERENONE (eplerenone) Product Monograph. Mint Pharmaceuticals Inc. April 15, 2021. **7.** ASPIRIN® (acetylsalicylic acid) Product Monograph. Bayer Inc. July 18, 2019. **8.** COVERSYL® (perindopril) Product Monograph. Servier Canada Inc. July 9, 2019. **9.** APO-FUROSEMIDE (furosemide) Product Monograph. Apotex Inc. July 13, 2018. **10.** APO-METFORMIN ER (metformin extended-release) Product Monograph. Apotex Inc. January 12, 2017. **11.** DIOVAN® (valsartan) Product Monograph. Novartis Pharmaceuticals Canada Inc. May 12, 2015. **12.** ATORVASTATIN (atorvastatin) Product Monograph. Sanis Health Inc. July 28, 2020. **13.** APO-BISOPROLOL (bisoprolol) Product Monograph. Apotex Inc. January 6, 2017. **14.** FORXIGA® (dapagliflozin) Product Monograph. AstraZeneca Canada Inc. June 29, 2020. **15.** Novartis Data on File – PARADIGM. 2020. **16.** 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.

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:

The 2021 CCS HF Guidelines recommend ARNI as a standard therapy for HFrEF, in combination with other standard therapies[16‡]

Consider ENTRESTO® in your patients with HFrEF

ACEi=angiotensin-converting-enzyme inhibitor; ARB=angiotensin receptor blocker; ARNI=angiotensin receptor-neprilysin inhibitor; CCS=Canadian Cardiovascular Society; CV=cardiovascular; HF: heart failure; HFrEF: heart failure with reduced ejection fraction.

* The primary endpoint was defined as the time-to-first-event.

† Clinical significance unknown.

‡ Please consult guidelines for complete recommendations.

Novartis Pharmaceuticals Canada Inc.
Dorval, Québec H9S 1A9
www.novartis.ca
T: 514.631.6775 F: 514.631.1867

131257E January 2022

NOVARTIS

MEMBER OF INNOVATIVE MEDICINES CANADA

REVIEWED BY PAAB

Pr Entresto® sacubitril/valsartan