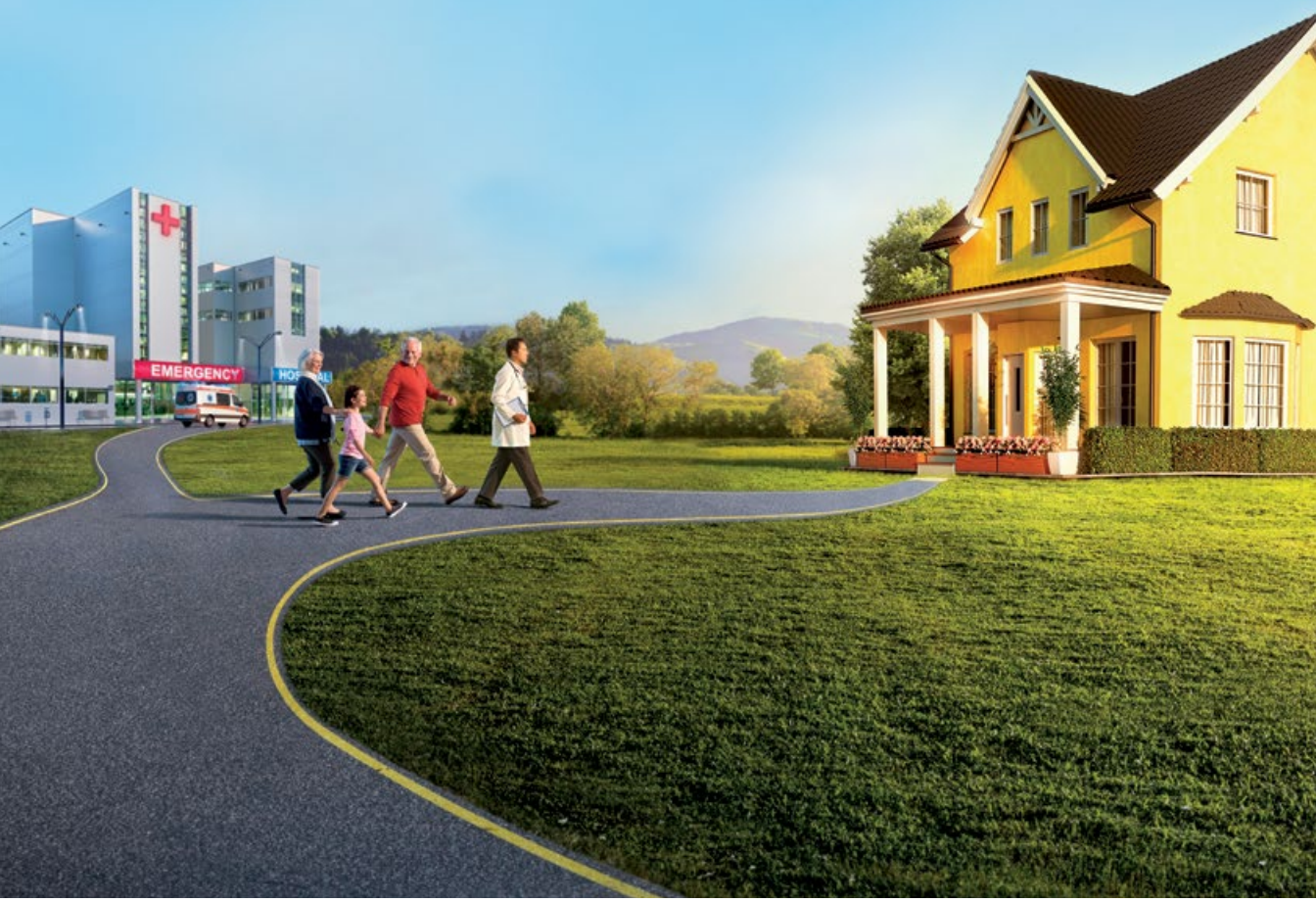
Trust the experience of ENTRESTO®
71,000 Canadian patients
have been treated
with ENTRESTO®[1]*†

For your patients with heart failure, consider

PrENTRESTO®

To reduce the incidence of heart failure hospitalization and cardiovascular (CV) death[2,3]



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 CV death and heart failure hospitalization.[2]

NYHA = New York Heart Association

* As of July 2021.
† Clinical significance is unknown.

PrEntresto®
sacubitril/valsartan

PARADIGM-HF trial:
The largest published clinical trial in chronic heart failure[4]*

Evaluation of the treatment effect of ENTRESTO®†

in 8,442 adult patients with reduced ejection fraction (LVEF ≤40%) and symptomatic chronic CHF (NYHA Class II-IV).[2]
ENTRESTO® is only indicated for use in NYHA Class II or III.

	PARADIGM-HF: Treatment Effect Results	Risk Reduction
Primary endpoint	**Time-to-first HF hospitalization or CV death** ENTRESTO® demonstrated clinically relevant and statistically significant superiority to enalapril for combined CV death or first HF hospitalization† (HR: 0.80 [95% CI: 0.73-0.87]; $p=0.0000002$‡) ENTRESTO® (914/4,187) vs. Enalapril (1,117/4,212)	20% HR: 0.80 [95% CI: 0.73-0.87] $p=0.0000002$‡
Components of primary endpoint	**First HF hospitalization** (HR: 0.79 [95% CI: 0.71-0.89]; $p=0.00004$‡) ENTRESTO® (537/4,187) vs. Enalapril (658/4,212)	21% HR: 0.79 [95% CI: 0.71-0.89] $p=0.00004$‡
	CV death§ (HR: 0.80 [95% CI: 0.71-0.89]; $p=0.00004$‡) ENTRESTO® (558/4,187) vs. Enalapril (693/4,212)	20% HR: 0.80 [95% CI: 0.71-0.89] $p=0.00004$‡

The primary endpoint was defined as the time-to-first-event.
Adapted from the ENTRESTO® Product Monograph and McMurray *et al*.[2,3]

Demonstrated safety and tolerability profile

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.[2¶]

Summary of adverse events of interest occurring in ≥5% of patients during the randomized, double-blind phase of PARADIGM-HF¶

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 renal failure	4.9	5.6

ENTRESTO® dosed up to 97 mg sacubitril/103 mg valsartan BID. Enalapril dosed up to 10 mg BID.
Adapted from the ENTRESTO® Product Monograph.[2]

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%).[2]

HF = heart failure; LVEF = left-ventricular ejection fraction; CHF = congestive heart failure
* Comparative clinical significance is unknown.
† The PARADIGM-HF trial was a multinational, randomized, double-blind trial comparing ENTRESTO® to enalapril. 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 ACE inhibitor or 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 ACE inhibitor 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® containing 49 mg sacubitril/51 mg valsartan (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® containing 97 mg sacubitril/103 mg valsartan (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 median follow-up duration of double-blind treatment was 27 months, with some patients treated for up to 4.3 years.[2]
‡ p-values one-sided as prespecified.
§ CV death includes all patients who died up to the cut-off date irrespective of previous hospitalization.
¶ 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%).[2]

Indication and clinical use:[2]

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 death and heart failure hospitalisation.

ENTRESTO® should be administered in combination with other heart failure therapies, in place of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (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:[2]

- 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/1.73m^2.
- Pregnant and nursing women.
- Hypersensitivity to the active substances, sacubitril or valsartan, or to any of the excipients.

Most serious warnings and precautions:[2]

- **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 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:[2]

- 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, a decision should be made whether to abstain from breastfeeding or to discontinue ENTRESTO® while breastfeeding, 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/1.73m^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.

References: 1. Novartis Data on File - Experience. 2021. **2.** ENTRESTO® Product Monograph. Novartis Pharmaceuticals Canada Inc. July 13, 2021. **3.** McMurray JJ, Packer M, Desai AS *et al.* Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med.* 2014;371(11):993-1004. **4.** Novartis Data on File – PARADIGM. 2020.

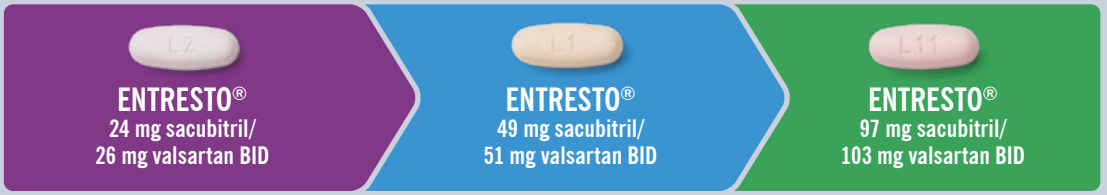
Initiating and titrating ENTRESTO® to target dose[2]

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**



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**

After 2-4 weeks as tolerated by patient

SBP = systolic blood pressure

Adapted from the ENTRESTO® Product Monograph[2]

Stop ACE inhibitor therapy for a 36-hour washout.[2]

ENTRESTO® must **not** be started until **36 hours have passed following discontinuation of ACE inhibitor therapy**.[2]

If patients experience tolerability issues, e.g. symptomatic hypotension or hyperkalemia, consideration should be given to temporary down-titration or treatment interruption of ENTRESTO®.[2]

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.[2]

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.[2]

ENTRESTO® should be used in place of an ACE inhibitor or ARB.[2]

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