To reduce the incidence of heart failure hospitalization and cardiovascular (CV) death

For your patients with heart failure, consider

**ENTRESTO®**

To reduce the incidence of heart failure hospitalization and cardiovascular (CV) death

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.

**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)

**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:

ENTRESTO® should only be started until 36 hours have passed following discontinuation of ACE inhibitor therapy.

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.

**ENTRESTO®** should be used in place of an ACE inhibitor or ARB.
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).1 ENTRESTO® is only indicated for use in NYHA Class II or III.

PARADIGM-HF trial: The largest published clinical trial in chronic heart failure

PARADIGM-HF: Treatment Effect Results

<table>
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<th>Primary endpoint</th>
<th>ENTRESTO® (553/4,187)</th>
<th>Enalapril (658/4,212)</th>
<th>Hazard Ratio</th>
<th>p-value</th>
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<td>Time-to-first HF hospitalization or CV death</td>
<td>ENTRESTO® demonstrated clinically relevant and statistically significant superiority to enalapril for combined CV death or first HF hospitalization.</td>
<td>ENTRESTO® (194/4,187) vs. Enalapril (1,117/4,212) Hazard Ratio (95% CI): 0.80 (0.73-0.87), p=0.000002‡</td>
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<tr>
<td>Renal failure, including acute</td>
<td>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</td>
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Primary endpoint

**Components of primary endpoint**

First HF hospitalization

ENTRESTO® (553/4,187) vs. Enalapril (658/4,212) Hazard Ratio (95% CI): 0.79 (0.71-0.88), p=0.000004

CV death

ENTRESTO® (553/4,187) vs. Enalapril (653/4,212) Hazard Ratio (95% CI): 0.80 (0.71-0.90), p=0.000004

**Summary of adverse events of interest occurring in ≥5% of patients during the randomized, double-blind period of the trial may be lower than those expected to be seen in actual clinical practice.2**

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

**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.
- 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 I or 2, or in patients with moderate to severe renal impairment, i.e., eGFR < 60 mL/min/1.73m²
- Pregnancy 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 ≥ 5.5 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, hypoadosteronism, or a high potassium intake in their diet.
- Decreases in renal function in susceptible individuals. Closely monitor serum creatinine, and dose-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 discontinue breastfeeding or to discontinue ENTRESTO® while breastfeeding, taking into account the importance of ENTRESTO® to the mother.
- A starting dose of 4 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/1.73m²).

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.

Adapted from the ENTRESTO® Product Monograph and McMurray et al.1

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Starting dose Target dose

ENTRESTO®
24 mg sacubitril/ 26 mg valsartan BID
After 2–4 weeks as tolerated by patient

ENTRESTO®
49 mg sacubitril/ 51 mg valsartan BID
After 2–4 weeks as tolerated by patient

ENTRESTO®
97 mg sacubitril/ 103 mg valsartan BID
After 2–4 weeks as tolerated by patient

Stop ACE inhibitor therapy for a 36-hour washout.

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

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Trust the experience of ENTRESTO®
36,000 Canadian patients
have been treated with ENTRESTO®

* As of November 2019
† Clinical significance is unknown.