To discuss clinical trials (e.g., PARADIGM-HF, the largest ever conducted trial to date in chronic heart failure patients[7]*) for ENTRESTO® or for resources/reprints of the CCS Heart Failure Guidelines, don't hesitate to contact your Novartis representative.

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.

* Comparative clinical significance has not been established.
CCS = Canadian Cardiovascular Society.

References: 1. Novartis Data on File – First and only. 2021. **2.** ENTRESTO® Product Monograph. Novartis Pharmaceuticals Canada Inc. July 13, 2021. **3.** Volpe M, *et al.* The natriuretic peptides system in the pathophysiology of heart failure: From the molecular basis to treatment. *Clin Sci (Lond).* 2016;130(2):57-77. **4.** Fielitz J, *et al.* Neutral endopeptidase is activated in cardiomyocytes in human aortic valve stenosis and heart failure. *Circulation.* 2002;105:286-289. **5.** Novartis Data on File – Patients treated. 2021. **6.** McDonald 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. **7.** Novartis Data on File – PARADIGM. 2020.

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

NOVARTIS

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MEMBER OF INNOVATIVE MEDICINES CANADA

REVIEWED BY PAAB

Pr Entresto® sacubitril/valsartan

PrENTRESTO®: The first and only treatment in its class (ARNI)[1]*

ENTRESTO® exerts cardiovascular and renal effects utilizing a dual approach[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 hospitalization.

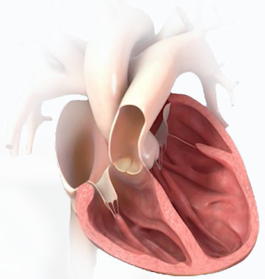
ENTRESTO® should be administered in combination with other heart failure therapies, in place of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB).

* Comparative clinical significance has not been established.
† Clinical significance has not been established.
ARNI = angiotensin receptor-neprilysin inhibitor; NYHA = New York Heart Association.

Pr Entresto® sacubitril/valsartan

Angiotensin II and the natriuretic peptide (NP) system are two pathways involved in HFrEF[2-4]

Increased angiotensin II activity
Prolonged angiotensin II activity contributes to the pathophysiology of HF



Increased neprilysin activity (and reduced NP levels)
Expression and activation of neprilysin are increased in patients with HF, which may contribute to degradation of NPs

ENTRESTO®: Dual-component mechanism of action*

Valsartan
INHIBITS angiotensin II
through AT_1 receptor blockade

Vasodilation, inhibition of renin/ aldosterone release

ENTRESTO®
(sacubitril + valsartan)

ARNI acts on **both** angiotensin II and the NP system via these two mechanisms

Sacubitril
INCREASES levels of NPs
by inhibiting their degradation by neprilysin

Vasodilation, natriuresis, and diuresis

Adapted from the ENTRESTO® Product Monograph.[2]

* Clinical significance has not been established.
† As of July 2021.
‡ Please consult guidelines for complete recommendations.[6]
ACEi=angiotensin-converting-enzyme inhibitor; ARB=angiotensin receptor blocker; ARNI=angiotensin receptor-neprilysin inhibitor; AT_1=angiotensin II Type-1; CCS=Canadian Cardiovascular Society; GDMT=guideline-directed medical therapy; HFrEF=heart failure with reduced ejection fraction.

Trust the experience of ENTRESTO®: 71,000 Canadian patients have been treated with ENTRESTO®[5]*†

ARNI: As recommended by the 2021 CCS Heart Failure Guidelines[6‡]

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.

The 2021 CCS HF Guidelines recommend ARNI be used in place of an ACEi or ARB, in patients with HFrEF, that remain symptomatic despite treatment with appropriate doses of GDMT…
(was assigned strong recommendation, high-quality evidence).