The HCP guide **to replacing ACEi/ARB with ENTRESTO®**

IN MOST PATIENTS WITH HFrEF:

Help Heart Failure Meet Heart Success with ENTRESTO

Not an actual patient.

Replace ACEi/ARB with ENTRESTO to help reduce the risk of CV death and HF hospitalization[1]*

*In the 2022 AHA/ACC/HFSA HF Guideline, ENTRESTO is recommended as a first-line treatment and to replace well-tolerated ACEi/ARB in patients with NYHA Class II—III HFrEF (Class 1 recommendation).

ACC, American College of Cardiology; ACEi, angiotensin-converting enzyme inhibitor; AHA, American Heart Association; ARB, angiotensin II receptor blocker; HFSA, Heart Failure Society of America; NYHA, New York Heart Association.

INDICATION

ENTRESTO is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal.

LVEF is a variable measure, so use clinical judgment in deciding whom to treat.

IMPORTANT SAFETY INFORMATION

WARNING: FETAL TOXICITY

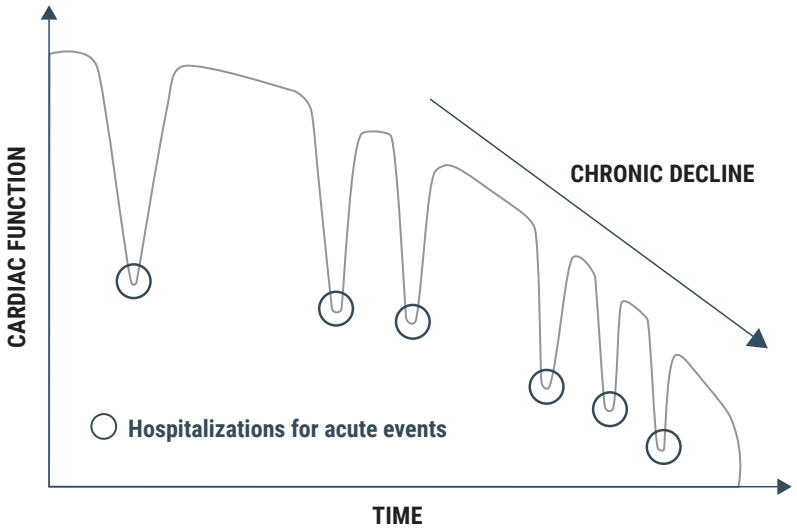
- **When pregnancy is detected, discontinue ENTRESTO as soon as possible**
- **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus**

Please see additional Important Safety Information throughout and **click here** for full Prescribing Information, including **Boxed WARNING**.

Entresto®
(sacubitril/valsartan) tablets
24/26mg • 49/51mg • 97/103mg

Heart failure is a continuous, progressive disease—are your patients' therapies optimized?

EVEN IF YOUR HF PATIENTS SEEM CLINICALLY STABLE, THEIR UNDERLYING DISEASE MAY BE PROGRESSING[2-4]



Adapted from Mesquita ET, Jorge AJL, Rabelo LM, et al. *Int J Cardiovasc Sci*. 2017;30(1):81—90.
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- Sudden cardiac death accounts for 40% to 45% of all deaths in HFrEF patients[5]
- In a study with a median follow-up of 27 months, 1 hospitalization put HFrEF patients at up to 6x greater risk of death vs those who had not been hospitalized for HFrEF[6,7]*

CONVERSATION STARTER

The progressive nature of heart failure comes with the risk of hospitalization and sudden cardiac death despite patients seeming to be clinically stable. What goals do your patients have for their treatment?

*Post hoc analysis of the PARADIGM-HF study, a multinational, randomized, double-blind trial comparing sacubitril/valsartan to enalapril in 8442 symptomatic (NYHA Class II—IV) HFrEF patients (LVEF ≤40%). For the primary end point, composite of CV death or first HF hospitalization, sacubitril/valsartan was superior to enalapril (*P*<.0001). This post hoc analysis examined the association of first nonfatal events—either HF hospitalization, ED visit, or outpatient intensification of HF therapy—with subsequent mortality during the trial. For the 1107 patients in the study who had a hospitalization for worsening HF as a first event, vs those with no event, the HR for mortality was 6.1 (95% CI: 5.4–6.8).

ED, emergency department; HR, hazard ratio.

IMPORTANT SAFETY INFORMATION (cont)

ENTRESTO® is contraindicated in patients with hypersensitivity to any component. ENTRESTO is contraindicated in patients with a history of angioedema related to previous angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy.

ENTRESTO is contraindicated with concomitant use of ACE inhibitors. Do not administer within 36 hours of switching from or to an ACE inhibitor. ENTRESTO is contraindicated with concomitant use of aliskiren in patients with diabetes.

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The 2022 AHA/ACC/HFSA HF Guideline strongly recommends ENTRESTO® in HFrEF[1]

In patients with chronic symptomatic **HFrEF*** who tolerate an ACEi/ARB, replacement by ENTRESTO is recommended to further reduce **MORBIDITY AND MORTALITY.**[1]

REPLACE

ACEi/ARB with ENTRESTO.
ACEi-treated patients require a 1.5-day washout period before initiating ENTRESTO

Class 1 recommendation to **REPLACE ACEi/ARB**[1†]

Not actual patients.

SOME SIGNALS THAT COULD INCREASE THE RISK OF HF HOSPITALIZATION[3,4]:

- A recent acute HF event
- Worsening symptoms
- Change in daily activities

*NYHA Class II–III patients with HFrEF.
†In NYHA Class II–III HFrEF patients who tolerate an ACEi/ARB.
‡In the 2022 HF Guideline, ENTRESTO is recommended as a first-line treatment and to replace well-tolerated ACEi/ARB in patients with NYHA Class II–III HFrEF (Class 1 recommendation).

RASi, renin-angiotensin system inhibitor.

Replace ACEi/ARB with ENTRESTO, the preferred RASi[1‡]

IMPORTANT SAFETY INFORMATION (cont)

Angioedema: ENTRESTO may cause angioedema. Angioedema associated with laryngeal edema may be fatal. ENTRESTO has been associated with a higher rate of angioedema in Black patients and in patients with a prior history of angioedema. ENTRESTO should not be used in patients with hereditary angioedema. If angioedema occurs, discontinue ENTRESTO immediately, provide appropriate therapy, and monitor for airway compromise. ENTRESTO must not be re-administered.

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Start ENTRESTO® with confidence

HOW TO PRESCRIBE ENTRESTO TO YOUR ADULT PATIENTS[7]

Choose initial dose of ENTRESTO, and after 2 to 4 weeks, titrate to the target dose, as tolerated by the patient.

ENTRESTO IS AVAILABLE IN 3 DOSAGE STRENGTHS[7]:

Low Starting Dose
24/26 mg BID

Recommended Starting Dose
49/51 mg BID

Target Dose
97/103 mg BID

Pills shown not actual size.

When switching from an ACEi, be sure to allow for a 1.5-day washout period prior to initiating ENTRESTO[7]

When switching from an ARB, start ENTRESTO at your patients' next scheduled dose[7]

- **ENTRESTO is contraindicated with concomitant use of an ACE inhibitor and in patients with a history of angioedema related to previous ACE inhibitor or ARB therapy**
- **Avoid use of ENTRESTO with an ARB, because ENTRESTO contains the angiotensin II receptor blocker valsartan**

The valsartan in ENTRESTO is more bioavailable than the valsartan in other marketed tablet formulations; 26 mg, 51 mg, and 103 mg of valsartan in ENTRESTO is equivalent to 40 mg, 80 mg, and 160 mg of valsartan in other marketed tablet formulations, respectively.

Please click here for additional important dosing information. For complete dosage and administration, always refer to the full Prescribing Information.

IMPORTANT SAFETY INFORMATION (cont)

Hypotension: ENTRESTO lowers blood pressure and may cause symptomatic hypotension. Patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), are at greater risk. Correct volume or salt depletion prior to administration of ENTRESTO or start at a lower dose. If hypotension persists despite dose adjustment of diuretics, concomitant antihypertensive drugs, and treatment of other causes of hypotension (e.g., hypovolemia), reduce the dosage or temporarily discontinue ENTRESTO. Permanent discontinuation of therapy is usually not required.

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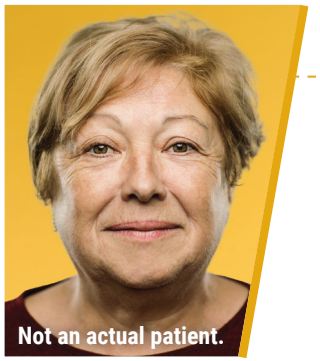
Are your HFrEF patients on optimal RASi therapy?

CONSIDER THIS HFrEF PATIENT*

Mildly symptomatic HFrEF patient (NYHA Class II)

Frances, 58 | **Experiencing mild symptoms with a modified lifestyle**



MEDICAL HISTORY	EXAMINATIONS AND TESTS	CURRENT TREATMENT
Diagnosed with HFrEF	**Echocardiogram: EF 35%**	**Valsartan**
Hospitalized in the last year	**Mild symptoms and slight limitations in activity**	**Metoprolol succinate**
	Blood pressure: 118/76 mm Hg	
	eGFR: 65 mL/min/1.73 m²	

HOW TO REPLACE THEIR ARB WITH ENTRESTO®[7]:

STOP Stop your patients' ARB

GO Start ENTRESTO at your patients' next scheduled dose

Strongest Class 1 recommendation in HFrEF as the preferred RASi to replace ACEi/ARB[1†]

CONVERSATION STARTER

Is your patient experiencing any HF symptoms? Are they new or ongoing? Worsening symptoms may indicate an increased risk of hospitalization. Review how your patient completed their symptom tracker to start the conversation.

*This profile is a hypothetical example of an eligible HFrEF patient. Please refer to the 2022 HF Guideline for complete guideline recommendations.

†In the 2022 HF Guideline, ENTRESTO is recommended as a first-line treatment and to replace well-tolerated ACEi/ARB in patients with NYHA Class II—III HFrEF (Class 1 recommendation).

EF, ejection fraction; eGFR, estimated glomerular filtration rate.

IMPORTANT SAFETY INFORMATION (cont)

Impaired Renal Function: Decreases in renal function may be anticipated in susceptible individuals treated with ENTRESTO. In patients whose renal function depends upon the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria, progressive azotemia and, rarely, acute renal failure and death. Closely monitor serum creatinine, and down-titrate or interrupt ENTRESTO in patients who develop a clinically significant decrease in renal function.

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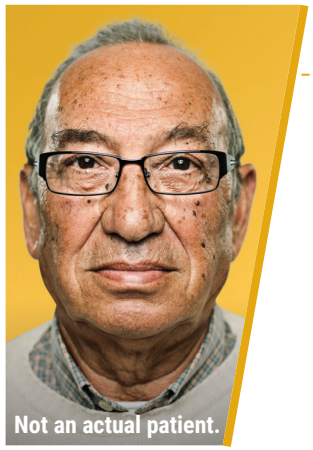
Can you optimize your patients' RASi therapy?

CONSIDER THIS HFrEF PATIENT*

Chronic, worsening HFrEF patient (NYHA Class III)

Edward, 69 | **Experiencing worsening HFrEF symptoms**



MEDICAL HISTORY	EXAMINATIONS AND TESTS	CURRENT TREATMENT
Diagnosed with HFrEF	Echocardiogram: EF 28%	Lisinopril
Moderate kidney disease	Marked limitation in activity	Chlorthalidone
Type 2 diabetes mellitus	eGFR: 45 mL/min/1.73 m²	Dapagliflozin
Hypertension	Blood pressure: 140/90 mm Hg	Metoprolol succinate
Recently hospitalized for an HF event within the last month		Metformin

HOW TO REPLACE THEIR ACEi WITH ENTRESTO®[7]:

STOP Stop your patients' ACE inhibitor

WAIT Wait for 1.5 days

GO Start ENTRESTO

Replace ACEi/ARB with ENTRESTO, the preferred RASi[1†]

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IMPORTANT SAFETY INFORMATION (cont)

Impaired Renal Function (cont): ENTRESTO may increase blood urea and serum creatinine levels in patients with bilateral or unilateral renal artery stenosis. In patients with renal artery stenosis, monitor renal function. Avoid use with aliskiren in patients with renal impairment (eGFR <60 mL/min/1.73 m²).

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs), including COX-2 inhibitors, with ENTRESTO may result in worsening of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically.

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ENTRESTO® support has options to help your eligible patients start and stay on therapy

OVER 80% OF PATIENTS HAVE NO PRIOR AUTHORIZATION AND THE LOWEST BRANDED CO-PAY[8]

ENTRESTO is available at the lowest branded co-pay for more than 99% of eligible Medicare patients[9]

30-day FREE TRIAL offer available for all eligible patients

Regardless of insurance, patients can access a 30-day free trial offer, pre-activated and ready to use when initiating treatment.

Limitations apply. This voucher is good for a 30-day (maximum 60 tablets; **one-time use**) free trial of ENTRESTO at no cost for your patient. Visit EntrestoHCP.com/support-and-resources to view Terms and Conditions.

$10 co-pay offer for eligible commercially insured patients

Your patients may pay as little as a $10 co-pay for up to a 90-day supply of ENTRESTO‡

The ENSPIRE Program from ENTRESTO®*

A free 12-month, personalized lifestyle and treatment support program† for your patients delivered by dedicated ENTRESTO Support Specialists covering the following topics and more:

- Dietary recommendations
- Heart-healthy lifestyle advice
- Medication management
- Tips and tools to manage symptoms
- Activity tracking

FOR YOUR PATIENTS WITH LIMITED OR NO PRESCRIPTION COVERAGE, THEY MAY QUALIFY FOR HELP FROM NOVARTIS PATIENT ASSISTANCE FOUNDATION (NPAF)

NPAF, a nonprofit organization, is committed to providing access to Novartis medications for those most in need. If your patient is experiencing financial hardship, has limited or no prescription coverage, and cannot afford the cost of their medications, then they may be eligible to receive Novartis medications for free. To learn more, call 1-800-277-2254 or visit www.PAP.Novartis.com.

*Must be 18 or older to enroll in the ENSPIRE Program from ENTRESTO®.
†Your patient can choose how they would like to be contacted, and they can opt out of any of these communications at any time.
‡Limitations apply. See Program Terms and Conditions. Eligible commercial patients pay as little as a $10 co-pay for each prescription fill (30-, 60-, 90-day fill) at retail or mail order. The program pays up to a $4100 cap across all fills per calendar year. Patient will be responsible for any co-pay once the $4100 limit is reached in a calendar year. This offer is not valid under Medicare, Medicaid, or any other federal or state program. See complete Terms and Conditions for details at EntrestoHCP.com/support-and-resources.

IMPORTANT SAFETY INFORMATION (cont)

Hyperkalemia: Hyperkalemia may occur with ENTRESTO. Monitor serum potassium periodically and treat appropriately, especially in patients with risk factors for hyperkalemia such as severe renal impairment, diabetes, hypoaldosteronism, or a high potassium diet. Dosage reduction or interruption of ENTRESTO may be required.

Concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium, may lead to increases in serum potassium.

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Concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium, may lead to increases in serum potassium.

ARBs: Avoid use of ENTRESTO with an ARB, because ENTRESTO contains the angiotensin II receptor blocker valsartan.

Lithium: Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists. Monitor serum lithium levels during concomitant use with ENTRESTO.

Common Adverse Events: In a clinical trial of patients with heart failure with reduced ejection fraction, the most commonly observed adverse events with ENTRESTO vs enalapril, occurring at a frequency of at least 5% in either group, were hypotension (18%, 12%), hyperkalemia (12%, 14%), cough (9%, 13%), dizziness (6%, 5%), and renal failure/acute renal failure (5%, 5%). No new adverse reactions were identified in a trial of the remaining indicated population.

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References

1. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. *J Am Coll Cardiol*. 2022;79(17):e263-e421. doi:10.1016/j.jacc.2021.12.012 **2.** Sabbah HN. Silent disease progression in clinically stable heart failure. *Eur J Heart Fail*. 2017;19(4):469-478. doi:10.1002/ejhf.705 **3.** Gheorghiade M, De Luca L, Fonarow GC, Filippatos G, Metra M, Francis GS. Pathophysiologic targets in the early phase of acute heart failure syndromes. *Am J Cardiol*. 2005;96(6A):11G-17G. doi:10.1016/j.amjcard.2005.07.016 **4.** Mesquita ET, Jorge AJL, Rabelo LM, Souza CV Jr. Understanding hospitalization in patients with heart failure. *Int J Cardiovasc Sci*. 2017;30(1):81-90. doi:10.5935/2359-4802.20160060 **5.** Masarone D, Limongelli G, Ammendola E, Verrengia M, Gravino R, Pacileo G. Risk stratification of sudden cardiac death in patients with heart failure: an update. *J Clin Med*. 2018;7(11):436. doi:10.3390/jcm7110436 **6.** Okumura N, Jhund PS, Gong J, et al. Importance of clinical worsening of heart failure treated in the outpatient setting: evidence from the prospective comparison of ARNi with ACEi to determine impact on global mortality and morbidity in heart failure trial (PARADIGM-HF). *Circulation*. 2016;133(23):2254-2262. doi:10.1161/circulationaha.115.020729 **7.** ENTRESTO [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp. **8.** Data on file. ENTRESTO Prior Authorization YTD. Novartis Pharmaceuticals Corp, 2021. **9.** Data on file. ENTRESTO 1SoT. Novartis Pharmaceuticals Corp; 2021. **10.** Senni M, McMurray JJV, Wachter R, et al. Initiating sacubitril/valsartan (LCZ696) in heart failure: results of TITRATION, a double-blind, randomized comparison of two uptitration regimens. *Eur J Heart Fail*. 2016;18(9):1193-1202. doi:10.1002/ejhf.548

IMPORTANT SAFETY INFORMATION (cont)

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How to replace an ACEi/ARB with ENTRESTO®

- ENTRESTO is contraindicated in patients with a history of angioedema related to previous ACE inhibitor or ARB therapy
- ENTRESTO is contraindicated with concomitant use of an ACEi. Do not administer within 36 hours of switching from or to an ACEi
- Avoid use of ENTRESTO with an ARB because ENTRESTO contains the angiotensin II receptor blocker valsartan

SWITCHING FROM A LOWER DOSE OR NOT CURRENTLY ON AN ACEi OR ARB[7]:

Low-dose ACEi	**STOP ACEi** **Wait** 36 hours then switch to ENTRESTO	**STARTING DOSE** 24/26 mg twice daily, as tolerated by the patient. Follow up in 2 to 4 weeks	**TITRATE TO** 49/51 mg twice daily, as tolerated by the patient. Follow up in 2 to 4 weeks	**TITRATE TO TARGET DOSE** 97/103 mg twice daily, as tolerated by the patient
Low-dose ARB or no ACEi/ARB	**STOP ARB** **GO** Switch to ENTRESTO			

- **Low-dose ACEi:** total daily dose of ≤10 mg of enalapril or therapeutically equivalent dose of another ACEi (eg, lisinopril ≤10 mg; ramipril ≤5 mg)[10]
- **Low-dose ARB:** total daily dose of ≤160 mg valsartan or therapeutically equivalent dose of another ARB (eg, losartan ≤50 mg; olmesartan ≤10 mg)[10]

SWITCHING FROM A HIGHER DOSE OF AN ACEi OR ARB[7]:

High-dose ACEi	**STOP ACEi** **Wait** 36 hours then switch to ENTRESTO	**STARTING DOSE** 49/51 mg twice daily, as tolerated by the patient. Follow up in 2 to 4 weeks	**TITRATE TO TARGET DOSE** 97/103 mg twice daily, as tolerated by the patient
High-dose ARB	**STOP ARB** **GO** Switch to ENTRESTO		

- **High-dose ACEi:** total daily dose of >10 mg of enalapril or therapeutically equivalent dose of another ACEi (eg, lisinopril >10 mg; ramipril >5 mg)[10]
- **High-dose ARB:** total daily dose of >160 mg valsartan or therapeutically equivalent dose of another ARB (eg, losartan >50 mg; olmesartan >10 mg)[10]

DOSING IN PATIENTS WITH RENAL OR HEPATIC IMPAIRMENT[7]:

How to prescribe ENTRESTO for severe renal impairment (eGFR <30 mL/min/1.73 m^2) or moderate hepatic impairment (Child-Pugh B classification)

STARTING DOSE 24/26 mg twice daily, as tolerated by the patient. Follow up in 2 to 4 weeks	**TITRATE TO** 49/51 mg twice daily, as tolerated by the patient. Follow up in 2 to 4 weeks	**TITRATE TO TARGET DOSE** 97/103 mg twice daily, as tolerated by the patient

- No starting dose adjustment is needed for mild or moderate renal impairment
- No starting dose adjustment is needed for mild hepatic impairment. Use in patients with severe hepatic impairment is not recommended

A 1.5-day washout is NOT required for patients switching from an ARB to ENTRESTO.

IMPORTANT SAFETY INFORMATION (cont)

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