

Clinical Resource Guide: Entresto Use in Hospice Settings

INTRODUCTION

In the United States, cardiovascular disease claims a life every 37 seconds, and it is anticipated that the prevalence of heart failure will continue to increase to eight million Americans by 2030. The 2022 American Heart Association Heart Failure Guidelines advocate for the initiation or transition of all heart failure patients to an ARNI agent, such as Entresto, as a strategy to mitigate morbidity and mortality. Consequently, a growing number of hospice patients are now listed with Entresto on their medication regimen and pose a distinct challenge for hospice healthcare providers in determining appropriate coverage of this expensive medication.

PHARMACIST CORNER OBJECTIVES

- 1.) Explain Entresto's mechanism of action and its reasons for caution in hospice care.
- 2.) Review common symptoms experienced by HF patients while on hospice care.
- 3.) Review alternative treatment options to Entresto to address HF symptoms.

ENTRESTO MECHANISM OF ACTION & ROLE IN THERAPY

Sacubitril/valsartan, brand name Entresto, is a first in class angiotensin receptor and neprilysin inhibitor (ARNI). This combination product includes an angiotensin receptor blocker (ARB) in valsartan, along with a neprilysin inhibitor prodrug, sacubitril which increases vasodilation and diuresis while decreasing fibrosis of the heart tissue. AHA guidelines recommend Entresto use to reduce **morbidity and mortality** in patients with chronic, symptomatic heart failure (HF) with reduced ejection fraction (HFrEF).

ADDRESSING HEART FAILURE SYMPTOMS IN HOSPICE PATIENTS

A significant portion of the hospice population affected by heart failure falls under the New York Heart Association (NYHA) Class IV classification. These patients frequently struggle with daily activities, and experience discomfort with symptoms such as cough, shortness of breath, difficulty sleeping, swelling, weight gain, confusion, and loss of appetite.

In patients previously prescribed Entresto, a reevaluation of its place in therapy is warranted at the time of hospice as patient goals of care evolve, with a primary focus on achieving comfort and minimizing potential side effects. A renin-angiotensin-aldosterone system inhibitor (RAASI) agent may be suitable in certain cases, and the alternative options to Entresto not only mitigate potential side effects, but also

prove to be more cost-effective. Angiotensin-converting enzyme inhibitors (ACEIs) like lisinopril and angiotensin receptor blockers (ARBs) such as valsartan, when used alone, have demonstrated efficacy in improving dyspnea, fatigue, and other heart failure symptoms for a majority of patients. Importantly, when transitioning patients from an ARNI to an ACEI, there is a required washout period of 36 hours between the administration of the two drugs.

Patients experiencing symptomatic hypotension may necessitate a complete down-titration of all RAASI agents, including Entresto. While discontinuing these medications might not lead to acute cardiac deterioration in the final days of life for some patients, it is crucial to maintain stability through a regimen that prioritizes comfort and euvolemia, often emphasizing other cost-effective agents such as diuretics and beta blockers.

See table below for an example of a patient regimen prior to hospice and a potential alternative once in hospice care.

EXAMPLE HOSPICE REGIMEN

GDMT Agent	Use	Preferred Hospice Agent	Use	Transition Pearls
Valsartan/Sacubitril (ENTRESTO)	ARB Combination medication Induces vasodilation, natriuresis, and controls hypertension	Lisinopril	ACEI Controls hypertension via vasodilation	Allow 36-hour wash out between before lisinopril administration
Dapagliflozin (FARXIGA)	SGLT2I Reduces cardiac preload and afterload	Discontinue		May be stopped without taper, monitor for worsening HF symptoms
Metoprolol Succinate XL	Beta blocker Controls blood pressure and heart rate	Continue		Monitor patient HR, blood pressure, and mental alertness
Spirolactone	Aldosterone Antagonist Block aldosterone, increasing natriuresis	Continue as tolerated		Continue in combination with diuretic as tolerated. May discontinue as necessary
Furosemide	Loop Diuretic Maintains patient volume via natriuresis	Continue		Titrate dose as necessary to maintain euvolemia

ALTERNATIVE AGENTS FOR MANAGEMENT OF HEART FAILURE

Alternative Treatment Strategies					
ACEI/ARBs					
Medication	Description	Contraindications	Dosing	Adverse Effects	Cost/fill Estimate (\$=<\$10.00) (\$\$=<\$20.00) (\$\$\$=<\$30.00)
Lisinopril	<ul style="list-style-type: none"> ACEI Avoid abrupt withdrawal Monitor renal function and potassium 	<ul style="list-style-type: none"> History of angioedema Bilateral renal artery stenosis Symptomatic hypotension (SBP<80 mmhg) Hyperkalemia sCr >3 	2.5-40 mg daily	<ul style="list-style-type: none"> Hypotension Increase sCr Increase K Cough Angioedema risk 	\$
Enalapril			2.5-20 mg daily		\$\$
Ramipril			1.25-10 mg daily		\$\$
Captopril			6.25- 50 mg TID		\$\$\$
Losartan	<ul style="list-style-type: none"> ARBs Avoid abrupt withdrawal Monitor renal function and potassium 	<ul style="list-style-type: none"> History of angioedema Bilateral renal artery stenosis Symptomatic hypotension (SBP<80 mmhg) Hyperkalemia sCr >3 	25-150 mg daily	<ul style="list-style-type: none"> Hypotension Increase sCr Increase K Cough Angioedema risk 	\$\$
Valsartan			40-160 mg BID		\$\$\$
Entresto (sacubitril/ valsartan)	<ul style="list-style-type: none"> ARNI Fixed combination product 36-hour washout required when transitioning to or from an ACEI Monitor renal function and potassium 	<ul style="list-style-type: none"> History of angioedema Concomitant use of aliskiren Symptomatic hypotension (SBP<100 mmhg) Hyperkalemia Renal dysfunction 	49/51 mg - 97/103 mg BID	<ul style="list-style-type: none"> Hypotension Impaired renal function Dizziness Increase K Angioedema risk 	\$\$\$\$
Beta Blockers					
Metoprolol succinate (XL)	<ul style="list-style-type: none"> Avoid abrupt withdrawal Monitor vital signs closely 	<ul style="list-style-type: none"> Acute volume overload Reactive airway disease Second- or third-degree AV block Severe bradycardia Severe hypotension (SBP<80 mmHg) 	12.5-200 mg daily	<ul style="list-style-type: none"> Fluid retention (monitor weight) Fatigue Bradycardia Hypotension 	\$\$
Carvedilol			3.125 mg-50 mg BID		\$\$
Bisoprolol			1.25-10 mg daily		\$\$\$\$
Loop Diuretics					
Bumetanide	<ul style="list-style-type: none"> Torsemide and bumetanide have increased oral bioavailability Highly individualized dosing Monitor patient I/O's, daily weights Drug interactions may effect response 	<ul style="list-style-type: none"> Hypokalemia Severe hyponatremia Hypotension Azotemia Anuria 	0.5-10 mg daily	<ul style="list-style-type: none"> Dizziness Headache GI upset Hypokalemia Hyponatremia Hypotension 	\$\$\$\$
Furosemide			20-600 mg daily		\$
Torsemide			10-200 mg daily		\$\$

SUMMARY

The role of Entresto and its considerations for caution in hospice care, underscores the need for a careful and individualized patient approach. New hospice patients with Entresto most likely will require therapy reassessment as their goals of care evolve, particularly when recentering goals from a curative perspective to a focus on comfort and the minimization of side effects. While Entresto may be suitable in some rare cases, cost-effective alternatives such as ACEIs and ARBs alone have demonstrated efficacy in improving heart failure symptoms. For some patients, a straightforward interchange to a comparable agent may be appropriate to fully address their symptoms, while for others the potential for symptomatic hypotension may necessitate a careful down-titration of all RAASI agents. Regardless of RAASI agent adjustments, it is crucial to recognize the importance of maintaining stability and comfort through agents like diuretics and beta blockers in combination with the core hospice comfort medications.

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