Sacubitril/Valsartan (Entresto®) Clinical and Reimbursement Information

Medicines Management Programme

Prescribing Tips and Tools

- ❑ **Class of Medicine-** Sacubitril/valsartan (Entresto®) is the first in a class of medicine known as **Angiotensin Receptor Neprilysin Inhibitor (ARNI).**
- ❑ **Therapeutic indication-** Sacubitril/valsartan is licensed in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction (HF-rEF).
- ❑ **Place in therapy**- Sacubitril/valsartan is given in conjunction with other HF therapies, in place of an angiotensin converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB).
- ❑ **Initiation**- Treatment with sacubitril/valsartan should be initiated by a **Heart Failure Specialist** with access to a multidisciplinary HF team.
- ❑ **Reimbursement**- Clinicians are required to apply for reimbursement approval via the Primary Care Reimbursement Service (PCRS) on an individual patient basis (see below).

SUMMARY OF CLINICAL-EFFECTIVENESS, CLINICAL GUIDELINES AND COST

Clinical effectiveness- PARADIGM-HF study

- **Study design-** Multinational, randomised, double-blind trial of 8,442 adult patients with New York Heart Association (NYHA) Class II to IV HF with a left ventricular ejection fraction (LVEF) of ≤ 40% (later amended to ≤ 35%)
- **Primary endpoint-** A composite of cardiovascular (CV) mortality or a first hospitalisation for HF
- **Objective-** To evaluate the effect of sacubitril/valsartan 97/103 mg compared to enalapril 10 mg in addition to conventional HF-rEF treatment, on time to occurrence of the primary endpoint
- **Results-** Sacubitril/valsartan was significantly more effective versus enalapril at reducing the risk of first hospitalisation for HF **(RRR 21%)**, CV mortality **(RRR 20%)** and all-cause mortality **(RRR 16%)**

Clinical guidelines

➢ **National Institute for Health and Care Excellence (NICE) Guideline TA388 (2018)**

Sacubitril/valsartan is recommended as an option for treating symptomatic chronic HF-rEF only in patients:

- with NYHA Class II to IV symptoms, **AND**
- with a LVEF of ≤ 35%, **AND**
- who are already taking a stable dose of an ACE inhibitor or an ARB

Treatment should be initiated by a HF Specialist with access to a multidisciplinary HF team

➢ **European Society of Cardiology (ESC) Guidelines (2021)**

The guideline recommends the use of an ARNI as a replacement for an ACE inhibitor in suitable patients who remain symptomatic on an ACE inhibitor, beta-blocker and a mineralocorticoid receptor antagonist (MRA), however an ARNI may be considered as a first-line therapy instead of an ACE inhibitor. The quality of evidence for an ACE inhibitor (Level A) is recognised as greater than the quality of evidence for an ARNI (Level B). See full guidelines for further information.

Cost

Annual cost comparison of ACE Inhibitor, ARBs and ARNI at optimal heart failure doses

ACE/ARB/ARNI treatment options at optimal heart failure doses			Annual cost*
ACE inhibitor	Ramipril 10 mg	once daily	€43.68
ARB	Candesartan 32 mg	once daily	€101.92
ARB	Valsartan 160 mg	twice daily	€109.20
ARNI	**Sacubitril/Valsartan 97/103 mg**	**twice daily**	**€1,677.00**

*PCRS reimbursement price (excluding fees). Prices correct as of 01/03/2022.

References

- Entresto® (Sacubitril/valsartan) tablets SmPC. Accessed at www.hpra.ie on 24/01/2022.
- McMurray JJV, Packer M, Desai AS et al. Angiotensin-Neprilysin Inhibition versus Enalapril in Heart Failure. *N Eng J Med* 2014;**371**:993-1004.
- Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction. NICE technology appraisal guidance No.388 (2018) on 24/01/2022.
- McDonagh TA, Metra A, Adamo M et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal 2021; 42: 3599-3726.
- PCRS list of reimbursable items. Accessed at www.pcrs.ie on 01/03/2022.

CRITERIA FOR REIMBURSEMENT APPROVAL OF SACUBITRIL/VALSARTAN

- To be eligible for reimbursement patients must meet the following criteria:
  - ✓ LVEF of ≤ 35%
  - ✓ Symptomatic with NYHA functional class II to IV symptoms
  - ✓ Receiving optimal medical therapy for HF including ACE inhibitor or an ARB (and other HF therapies including a beta-blocker and MRA as necessary)
  - ✓ Systolic blood pressure ≥ 100 mmHg
  - ✓ Serum potassium (K+) ≤ 5.4 mmol/L
- Clinicians are required to apply for reimbursement approval on an individual patient basis. The clinician responsible for the **initiation** of treatment should ensure that the patient has received reimbursement approval prior to issuing a prescription.
- Clinicians have **one** opportunity to submit an online application on behalf of each individual patient.
- In the case of a negative reimbursement recommendation, an appeal can be sent directly to the HSE-Medicines Management Programme (MMP) at mmp@hse.ie, addressing the rejection reason(s) and outlining any additional information.

CONTRAINDICATIONS FOR USE

- ✕ Hypersensitivity to sacubitril, valsartan or any of the excipients (See SmPC Entresto®)
- ✕ Concomitant use with ACE inhibitors
- ✕ History of angioedema related to treatment with previous ACE inhibitor or ARB
- ✕ Hereditary or idiopathic angioedema
- ✕ Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or with eGFR < 60ml/min/1.73m²
- ✕ Severe hepatic impairment, biliary cirrhosis and cholestasis
- ✕ Second and third trimesters of pregnancy

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

- ✕ Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
- ✕ Systolic blood pressure < 100 mmHg
- ✕ Impaired renal function (eGFR < 30 ml/min/1.73m²) or worsening renal function
- ✕ Bilateral or unilateral renal artery stenosis
- ✕ Potassium level (K+) > 5.4 mmol/L
- ✕ Angioedema
- ✕ NYHA Class IV- limited clinical experience
- ✕ Moderate hepatic impairment
- ✕ First trimester of pregnancy
- ✕ Psychiatric events such as hallucinations, paranoia and sleep disorders, in context of psychotic events, have been associated with sacubitril/valsartan use.

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Sacubitril/Valsartan (Entresto®) Prescribing Tips and Tools

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DOSAGE FORM AND STRENGTHS

Sacubitril/valsartan under the brand Entresto® is a film-coated tablet given TWICE DAILY.
There are three strengths available: 24/26 mg, 49/51 mg, 97/103 mg.

The bioavailability of valsartan in ENTRESTO® differs from other marketed valsartan formulations and the equivalent doses are shown below.

Comparison of the valsartan strength in Entresto® and the equivalent dose in currently marketed valsartan

Strength of sacubitril/valsartan preparation	Valsartan dose in sacubitril/valsartan	Equivalent dose in marketed valsartan
Entresto® 24/26 mg (SPECIAL POPULATIONS, see below)	**26 mg twice daily**	**40 mg twice daily**
Entresto® 49/51 mg (RECOMMENDED STARTING DOSE)	**51 mg twice daily**	**80 mg twice daily**
Entresto® 97/103 mg (MAINTENANCE DOSE)	**103 mg twice daily**	**160 mg twice daily**

When prescribing always use the standard dose format according to the summary of product characteristics (SmPC)

To avoid confusion, always prescribe generically & write doses of individual components clearly

INITIATION AND DOSE TITRATION

- **Sacubitril/valsartan (Entresto®) should be initiated by a HEART FAILURE SPECIALIST**
- **For special precautions & contraindications (see overleaf) and refer to Entresto® SmPC for full details**

ENTRESTO® MUST NOT BE ADMINISTERED UNTIL 36 HOURS AFTER DISCONTINUING ACE INHIBITOR NO WASHOUT IS NEEDED WHEN SWITCHING FROM ARB TO ENTRESTO®

Standard dosing for initiation and up-titration of eligible patients

STANDARD DOSING	Initiation Week 1	Week 2 to Week 3/4	Increase after 2 to 4 weeks from initiation to the target maintenance dose, as tolerated
Sacubitril/valsartan	49/51 mg twice daily	49/51 mg twice daily	97/103 mg twice daily

Special Populations – initiation and dosing

Certain special populations were not included in the PARADIGM-HF trial however SmPC for Entresto® provides guidance on initiation and dosing in these patient groups, which include:

- ✓ Moderate to severe renal impairment
- ✓ Moderate hepatic impairment
- ✓ Systolic blood pressure ≥ 100 mmHg to 110 mmHg
- ✓ Patients NOT currently taking or taking a LOW DOSE of an ACE inhibitor or ARB

A lower starting dose of sacubitril/valsartan (Entresto®) 24/26 mg is recommended in these patient groups and slower titration may also be recommended (refer to Entresto® SmPC for full details)

Initiation and up-titration in SPECIAL POPULATIONS (see list above)

SPECIAL POPULATIONS DOSING	Initiation Week 1	Week 2 to Week 3/4	Increase dose as recommended to the target maintenance dose as tolerated		
Sacubitril/valsartan	24/26 mg twice daily	24/26 mg twice daily	49/51 mg twice daily	2- 4 weeks*	97/103 mg twice daily

*A slow dose titration (doubling 3-4 weeks) is recommended in patients not currently taking an ACE inhibitor or ARB, or taking low doses of these agents

INTERACTIONS

Refer to Entresto® SmPC for full and detailed list of interactions

Co-administration Contraindicated		
ACE inhibitor	ARB	Aliskiren in patients with diabetes mellitus or renal impairment (eGFR < 60ml/min/1.73m²)

Co-administration Cautioned				
Statins	PDE-5 inhibitors	K+ sparing diuretics	Mineralocorticoid receptor antagonists	K+ supplements
NSAIDs	Furosemide	Lithium	COX-II inhibitors	Rifampicin
Nitrates	Ciclosporin	Ritonavir	Tenofovir	Metformin

ADVERSE DRUG REACTIONS

Refer to Entresto® SmPC for all adverse drug reactions

Very Common (≥1/10) and Common (≥1/100 to <1/10) Adverse Drug Reactions			
Very common	• Hyperkalaemia	• Renal Impairment	• Hypotension
Common	• Anaemia • Hypokalaemia • Syncope • Vertigo • Nausea	• Hypoglycaemia • Dizziness • Orthostatic Hypotension • Renal Failure • Fatigue	• Headache • Diarrhoea • Asthenia • Cough • Gastritis

ANGIOEDEMA has also been reported with sacubitril/valsartan. If angioedema occurs discontinue immediately and do not re-administer.

MONITORING

Refer to Entresto® SmPC for full and detailed list of monitoring requirements

Sacubitril/Valsartan Monitoring	
Blood pressure	Monitor BP when initiating & titrating especially in patients ≥ 65 years and patients with eGFR < 30ml/min/1.73m²
Serum K+	Monitor K+ especially with risk factors e.g. renal impairment, diabetes mellitus, high potassium diet and on concomitant mineralocorticoid receptor antagonists (spironolactone & eplerenone)
Renal function	Monitor renal function- avoid dehydration and use of NSAIDs. Monitor for hypotension

Advice for Patients / Patient Counselling

- ➢ Take twice daily morning and evening, with or without food
- ➢ Do not take for at least 36 hours after discontinuing ACE inhibitor therapy
- ➢ Seek immediate medical attention if you notice any swelling of the face, lips, tongue or throat. This may be a sign of angioedema
- ➢ Store in the original package to protect from moisture
- ➢ Avoid NSAIDs and COX-II inhibitors