▼ 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 new 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 heart failure (HF) team
- ❑ **Reimbursement**- Patients must be registered with the Primary Care Reimbursement Service (PCRS) prior to initiation of treatment for reimbursement to be authorised (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 97/103mg compared to enalapril 10mg 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 (2016)**

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 (2016)**

Sacubitril/valsartan is recommended to replace an ACE inhibitor to further reduce the risk of HF hospitalisation and death in patients with HF-rEF who remain symptomatic despite optimal treatment with an ACE inhibitor, a beta-blocker and an mineralocorticoid receptor antagonist (MRA)

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 10mg	once daily	€50.96
ARB	Candesartan 32mg	once daily	€118.04
ARB	Valsartan 160mg	twice daily	€109.20
ARNI	**Sacubitril/Valsartan 97/103mg**	**twice daily**	**€1,807.13**

*PCRS reimbursement price (excluding fees). Prices for ACE inhibitor and ARBs correct as of 1st October 2017. Sacubitril/valsartan reimbursement price from 1st December 2017.

▼ Entresto® is subject to additional monitoring. Healthcare professionals are particularly encouraged to report any suspected adverse reactions with medicines carrying this symbol to the HPRA so that any new/emerging safety information may be promptly identified and analysed.
Online reporting: www.hpra.ie. Email: medsafety@hpra.ie

CRITERIA FOR REIMBURSEMENT APPROVAL OF SACUBITRIL/VALSARTAN

- To be eligible for reimbursement patients must meet the following criteria:
  - ✓ LVEF of ≤35%, and
  - ✓ Symptomatic with NYHA functional class II to IV symptoms, and
  - ✓ 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 ≥100mmHg
  - ✓ Serum potassium (K+) ≤5.4mmol/L
- The patient must be registered with the PCRS by the clinician responsible for the **initiation** of treatment and received approval prior to issuing a prescription
- Clinicians must be User-Registered with the PCRS to access the online application system available at www.pcrs.ie > Online Services > Services for Hospitals > Special Drug Request User Registration form. Email cert.info@hse.ie for more details
- The online reimbursement application is accessible at www.pcrs.ie > Online Services > Services for Hospitals > Sacubitril/Valsartan reimbursement application

CONTRAINDICATIONS FOR USE

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

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

- x Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
- x Systolic blood pressure <100mmHg
- x Impaired renal function (eGFR <30ml/min/1.73m²) or worsening renal function
- x Bilaterial or unilaterial renal artery stenosis
- x Potassium level (K+) >5.4mmol/L
- x Angioedema
- x NYHA Class IV- limited clinical experience
- x Moderate hepatic impairment

References

- Entresto® (Sacubitril/valsartan) 49/51mg tablets SmPC. Date 19th November 2015. Accessed at www.hpra.ie on 18/10/2017.
- 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 (April 2016).
- Ponikowski P, Voors AA, Anker SD et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2016;**37**:2129-2200.
- PCRS list of reimbursable items. Accessed at www.pcrs.ie on 18/10/2017.

▼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: 24/26mg, 49/51mg, 97/103mg.

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® 24/26mg (SPECIAL POPULATIONS, see below)	**26mg twice daily**	**40mg twice daily**
Entresto® 49/51mg (RECOMMENDED STARTING DOSE)	**51mg twice daily**	**80mg twice daily**
Entresto® 97/103mg (MAINTENANCE DOSE)	**103mg twice daily**	**160mg 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	49/51mg twice daily	49/51mg twice daily	97/103mg 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 ≥100mmHg to 110mmHg
- ✓ Patients NOT currently taking or taking a LOW DOSE of an ACE inhibitor or ARB

A lower starting dose of sacubitril/valsartan (Entresto®) 24/26mg 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	24/26mg twice daily	24/26mg twice daily	49/51mg twice daily	2- 4 weeks*	97/103mg 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 (GFR<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