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Health Service Executive

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Circular No. 52/17

Reimbursement of Sacubitril/Valsartan (Entresto®) effective 1st December 2017

Dear Pharmacist,

The HSE has approved reimbursement for Sacubitril/Valsartan (Entresto®) 24mg/26mg, 49mg/51mg and 97mg/103mg film coated tablets under Community Drug Schemes from 1st December 2017. Sacubitril/Valsartan (Entresto®) is the first new class of medicine known as Angiotensin Receptor Neprilysin Inhibitor (ARNI) and is a combination of neprilysin inhibitor and an angiotensin II receptor blocker (ARB).

Due to the potential budget impact associated with this medicine, PCRS is introducing a reimbursement application system to ensure appropriate symptomatic chronic heart failure patients with reduced ejection fraction have access to this treatment. A separate communication has been issued to the hospital system in this regard. The reimbursement application must be made by the physician responsible for the initiation of treatment due to the mandatory information required for reimbursement to be approved. Whilst it is anticipated that the majority of patients will be initiated at hospital level due to laboratory tests and monitoring requirements, the product license does not preclude a GP from commencing a patient on treatment. Where the GP is making that therapeutic choice, he/she has the responsibility to enrol the patient for approval.

Approval can be confirmed through the 'Eligibility Confirmation' on the Pharmacy Application Suite under 'Patient Specific Arrangements'. Pharmacies can dispense and claim for Sacubitril/Valsartan (Entresto®) electronically using the product GMS code, submitting in the normal manner with monthly claims. Claims submitted for patients who are not approved will not be paid. Please note that patients currently accessing the medicine through a compassionate access programme will need online approval for ongoing reimbursement support from 1st December 2017.

The Medicines Management Programme (MMP) has developed a 'Tips and Tools' document to guide in the appropriate prescribing and monitoring of patients on Sacubitril/Valsartan (Entresto®) and is enclosed for your information.

Yours faithfully,

Anne Marie Hoey

Anne Marie Hoey
Primary Care Reimbursement & Eligibility

▼ 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

Medicines Management Programme

Prescribing Tips and Tools

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