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

<table>
<thead>
<tr>
<th>ACE/ARB/ARNI treatment options at optimal heart failure doses</th>
<th>Annual cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor Ramipril 10mg once daily</td>
<td>€50.96</td>
</tr>
<tr>
<td>ARB Candesartan 32mg once daily</td>
<td>€118.04</td>
</tr>
<tr>
<td>ARB Valsartan 160mg twice daily</td>
<td>€109.20</td>
</tr>
<tr>
<td>ARNI Sacubitril/valsartan 97/103mg twice daily</td>
<td>€1,807.13</td>
</tr>
</tbody>
</table>

*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.

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

- 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
- Pregnancy

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

- Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
- Systolic blood pressure <100mmHg
- Impaired renal function (eGFR <30ml/min/1.73m²) or worsening renal function
- Bilateral or unilateral renal artery stenosis
- Potassium level (K+) >5.4mmol/L
- Angioedema
- NYHA Class IV- limited clinical experience
- Moderate hepatic impairment
Sacubitril/valsartan (Entresto®) Prescribing Tips and Tools

**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

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

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

### Dosage Form and Strengths

<table>
<thead>
<tr>
<th>Strengths Available</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>24/26mg</td>
<td></td>
</tr>
<tr>
<td>49/51mg</td>
<td></td>
</tr>
<tr>
<td>97/103mg</td>
<td></td>
</tr>
</tbody>
</table>

### Initiation and Dose Titration

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

**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**

#### Standard dosing for initiation and up-titration of eligible patients

<table>
<thead>
<tr>
<th>STANDARD DOSING</th>
<th>Initiative Week 1</th>
<th>Week 2 to Week 3/4</th>
<th>Increase after 2 to 4 weeks from initiation to the target maintenance dose, as tolerated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sacubitril/valsartan</td>
<td>49/51mg twice daily</td>
<td>49/51mg twice daily</td>
<td>97/103mg twice daily</td>
</tr>
</tbody>
</table>

**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)

<table>
<thead>
<tr>
<th>SPECIAL POPULATIONS DOsing</th>
<th>Initiative Week 1</th>
<th>Week 2 to Week 3/4</th>
<th>Increase dose as recommended to the target maintenance dose as tolerated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sacubitril/valsartan</td>
<td>24/26mg twice daily</td>
<td>24/26mg twice daily</td>
<td>49/51mg twice daily</td>
</tr>
</tbody>
</table>

* 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

**Co-administration Contraindicated**

<table>
<thead>
<tr>
<th>Category</th>
<th>Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor</td>
<td>ARB</td>
</tr>
</tbody>
</table>

**Co-administration Cautioned**

<table>
<thead>
<tr>
<th>Category</th>
<th>Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>PDE-5 inhibitors</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Furosemide, Lithium, COX-II inhibitors, Rifampicin</td>
</tr>
</tbody>
</table>

### 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
- Hypoglycaemia
- Dizziness
- Orthostatic Hypotension
- Renal Failure
- Fatigue
- Cough
- Gastritis

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

### Monitoring

**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

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www.hse.ie/yourmedicines