

# Sacubitril with Valsartan (Entresto) for Heart Failure with reduced ejection fraction

## Fact Sheet

### What is Sacubitril/valsartan (Entresto)?

Sacubitril/valsartan (Entresto) is a medication in a new drug class called angiotensin receptor-neprilysin inhibitor (ARNI). Sacubitril (neprilysin inhibitor) increases vasodilatory peptides leading to greater sodium loss and decreases ventricular hypertrophy and remodelling. Valsartan is an angiotensin II receptor blocker (ARB) that inhibits neprilysin induced activation of the Renin Angiotensin Aldosterone System (RAAS).

### Indications

The Pharmaceutical Benefits Scheme (PBS) recommends Entresto for patients with Heart Failure who are symptomatic with NYHA class II-IV (evidence is limited for NYHA Class IV). The patient must have all of the following:

- A left ventricular ejection fraction (LVEF) less than or equal to 40%
- Be on concomitant optimal standard heart failure treatment, which must include the maximum tolerated dose of a beta-blocker (unless contraindicated or unable to tolerate)
- Be stabilised on an angiotensin-converting-enzyme inhibitor (ACEI) or ARB (unless contraindicated or unable to tolerate). NB. Entresto must not be co-administered with an ACEI or an ARB.

### Changing to Entresto

- From ACEI: stop ACEI, **wait at least 36 hours after last dose**, then start Entresto
- From ARB: stop ARB, no washout period required, can start Entresto when next dose would have been due

**CAUTION: Entresto MUST NOT be taken with an ACEI. *If this occurs: cease ACEI immediately; assess for possible angioedema; check blood pressure (BP), serum potassium (K+), renal function; and inform treating medical team.***

### Dosing

Dose is expressed as sacubitril (mg) /valsartan (mg). Some literature may also express the dose as: 50mg (24/26mg), 100mg (49/51mg) and 200mg (97/103mg). Dose equivalence: 26 mg valsartan in this fixed-dose combination is equivalent to 40 mg valsartan in other products.

Current ACEI/ARB dose	Initial Entresto dose	Entresto Titration
<b>Full dose</b>	49/51mg BD	Increase dose after 2-4 weeks to target dose of 97/103mg BD (or as tolerated)
<b>Low dose*</b>	24/26mg BD	Double dose every 4 weeks to target dose of 97/103mg BD (or as tolerated)

\*Low dose for those at high risk of hypotension; elderly (> 75 years); eGFR < 60mL/min; moderate hepatic impairment (Child-Pugh Class B) or if AST/ALT > twice ULN

### Available preparations

Generic name	Trade name	Tablets per script
<b>sacubitril 24 mg, valsartan 26 mg</b>	<i>Entresto 24/26</i>	56 tabs (1 month)
<b>sacubitril 49 mg, valsartan 51mg</b>	<i>Entresto 49/51</i>	56 tabs (1 month)
<b>sacubitril 97 mg, valsartan 103mg</b>	<i>Entresto 97/103</i>	56 tabs (1 month)

## Side-effects and Monitoring

Side Effects*	Monitoring
<b>Symptomatic hypotension</b>	BP at baseline and with each dose increase
<b>Hyperkalaemia</b>	Serum K <sup>+</sup> level at: baseline; one week after starting or changing dose; and every 3 to 6 months during stable maintenance in the absence of other risk factors.
<b>Renal impairment</b>	Renal function at: baseline; one week after starting or changing dose; and every 3 to 6 months during stable maintenance in the absence of other risk factors.
<b>Angioedema</b>	Stop Entresto immediately and indefinitely

\*Many side effects and required monitoring are similar to those of ACEI and ARB (see product information for a more comprehensive list)

## Precautions / Contraindications

Issue	Action
<b>Angioedema</b>	<ul style="list-style-type: none"> <li>• Avoid use in patients with a history of angioedema due to ACEI or ARB, hereditary or idiopathic angioedema</li> <li>• Do not use combination of ACEI or ARB with Entresto</li> <li>• <b>Ensure 36 hours washout period when switching from an ACEI</b></li> </ul>
<b>Hypotension</b>	<ul style="list-style-type: none"> <li>• Avoid use if systolic BP is less than 100mmHg</li> <li>• Use reduced starting dose in patients with systolic BP 100–110 mmHg or other risk factors for hypotension and monitor carefully</li> </ul>
<b>Elderly</b>	<ul style="list-style-type: none"> <li>• Use reduced starting dose in people over 75 years</li> </ul>
<b>Renal impairment</b>	<ul style="list-style-type: none"> <li>• Use reduced starting dose when eGFR is less than 60mL/min</li> <li>• Use cautiously if eGFR less than 30 mL/min (this group was excluded in the trial)</li> <li>• Use cautiously if at risk of hypovolaemia or if used with NSAIDs (including selective COX-2 inhibitors), as it can worsen renal impairment</li> <li>• Use cautiously in patients with bilateral renal artery stenosis</li> </ul>
<b>Hyperkalaemia</b>	<ul style="list-style-type: none"> <li>• Do not initiate if serum K<sup>+</sup> is greater than 5.4 mmol/L</li> </ul>
<b>Hepatic impairment</b>	<ul style="list-style-type: none"> <li>• Contraindicated in severe (Child-Pugh class C) hepatic impairment (no data)</li> <li>• Use cautiously and reduce starting dose in moderate hepatic impairment (Child-Pugh class B) or if AST/ALT is greater than twice ULN.</li> </ul>
<b>Women</b>	<ul style="list-style-type: none"> <li>• Use effective contraception during treatment with Entresto and for 1 week after stopping treatment</li> <li>• Avoid use in pregnancy or during lactation</li> </ul>
<b>Other Medicines</b>	<ul style="list-style-type: none"> <li>• ACEI/ARB: Do not use in combination with Entresto</li> <li>• Statins: In vitro data suggests that co-administration with statins may increase the systemic exposure of statins, increasing the risk of myopathy or rhabdomyolysis.</li> <li>• Use cautiously when administering with other medicines that may compromise BP, renal function, or cause electrolyte disturbances.</li> </ul>
<b>Storage</b>	<ul style="list-style-type: none"> <li>• Entresto tablets should be stored in the original packaging. There is no data supporting the stability of Entresto tablets once removed from the packaging. In the case of dose administration aids, the tablets could be included if still enclosed in the blister packaging.</li> </ul>

## References:

Pharmaceutical Benefits Scheme [www.pbs.gov.au](http://www.pbs.gov.au)

McMurray, J. J. et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N. Engl. J. Med.* 371, 993–1004 (2014).

Australian Medicines Handbook 2015 (online). Adelaide: Australian Medicines Handbook Pty Ltd; 2015 January. Available from:

<http://amhonline.amh.net.au/>

Entresto (2016). In MIMS Online. Retrieved from <http://www.mims.com.au>

Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically

Correspondence with Novartis Senior Specialist Representative Qld North 26/7/17 (Storage of Entresto)

Correspondence with Queensland Medicines Advice and Information Service 4/8/17 (Storage of Entresto)

This form is not intended to replace clinical judgement. Reviewed August 2017. Endorsed by Queensland Heart Failure Steering Committee.