Prescribing Protocol SESLHDPR/585 Sacubitril+Valsartan (Entresto®) in Systolic Heart Failure

Title	Sacubitril+Valsartan (Entresto®) for Systolic Heart Failure
Areas where Protocol/Guideline applicable	SESLHD
Authorised Prescribers	Only to be commenced by a Heart Failure specialist with access to a multidisciplinary team All medical officers may prescribe ongoing therapy
Indication for use	Chronic heart failure in patients who meet the following criteria: • Patient must be symptomatic with NYHA classes II, III or IV, AND • Patient must have a documented left ventricular ejection fraction (LVEF) of less than or equal to 40%, AND • Patient must receive concomitant optimal standard chronic heart failure treatment, which must include the maximum tolerated dose of a beta-blocker, unless contraindicated or not tolerated, AND • Patient must have been stabilised on an ACE inhibitor at the time of initiation with this drug, unless such treatment is contraindicated according to the TGA-approved Product Information or cannot be tolerated; OR • Patient must have been stabilised on an angiotensin II antagonist at the time of initiation with this drug, unless such treatment is contraindicated according to the TGA-approved Product Information or cannot be tolerated,
Clinical condition	Standard diagnosis for heart failure, including Echocardiogram (ECHO) to determine left ventricular ejection fraction (EF)% Patients diagnosed with chronic heart failure with reduced ejection fraction; • Ejection fraction (EF) < 40% • NYHA class II-IV • Concomitant treatment with optimal background treatment for heart failure including a beta-blocker (max tolerated dose) and prior use of ACE-I or ATRA

Contraindications	Concomitant use with an ACE inhibitor or angiotensin II antagonist. *Changing to sacubitril+valsartan:* • *stop ACEi, wait at least 36 hours after last dose before starting sacubitril+valsartan.* • *stop ARB, no washout period required, can start sacubitril+valsartan when next dose would have been due.* Known history of angioedema related to previous ACEi or ARB therapy. Hereditary or idiopathic angioedema. Severe hepatic impairment, biliary cirrhosis and cholestasis. Hypersensitivity to the active substance, sacubitril, valsartan or to any of the excipients. Concomitant use with aliskiren in patients with type 2 diabetes. Pregnancy – Category D
Precautions	Hypotension – Sacubitril+valsartan has not been studied in patients with systolic BP <100mmHg and use in these patients is not recommended. Impaired Renal Function - caution should be exercised when administering to patients with severe renal impairment (est. eGFR <30). There is no experience in patients with end stage renal disease and it is not recommended for these patients. Hyperkalaemia - If serum potassium level is >5.4mmol/L, consider discontinuing treatment. Angioedema - If angioedema occurs, sacubitril/valsartan should be discontinued and not be re-administered. Renal Artery Stenosis - Caution and monitoring of renal function is recommended. NYHA functional class IV - Caution recommended due to limited clinical data. Hepatic Impairment - Caution recommended in patients with moderate hepatic impairment (Child-Pugh B) or with ALT/AST >2 times upper limit of normal. .
Proposed Place in Therapy	Sacubitril + valsartan is a substitute for ACEi and ARBs as a second line treatment of systolic heart failure. It does not replace other first or second line therapies (i.e. beta blockers, diuretics, MRAs, digoxin or ivabradine).
If part of combination therapy, list other drugs	Concomitant treatment with optimal background treatment for heart failure including a beta-blocker (maximum tolerated dose) Other therapies could include MRA's, diuretics etc.

Dosage (Include dosage adjustment for specific patient groups)	The recommended starting dose is one tablet of 49 mg/51 mg twice daily. The dose should be doubled after 2 to 4 weeks to the target maintenance dose of one tablet of 97 mg/103 mg twice daily, as tolerated. Starting dose of 24 mg/26 mg taken twice daily is recommended for: - patients with risk factors for hypotension, including patients ≥ 75 years old and patients with low systolic blood pressure (SBP ≥100 to 110 mmHg). - patients not currently taking an ACE inhibitor or an ARB, or patients previously taking low doses of these agents, - patients with severe renal impairment (eGFR<30mL/min). Not recommended to use in end-stage renal disease. - Patients with moderate hepatic impairment (Child-Pugh B classification). Due to the potential risk of angioedema when used concomitantly with an ACE inhibitor, sacubitril+valsartan must not be administered until 36 hours after the last dose of ACE inhibitor therapy and similarly, at least 36 hours must elapse after the last dose of sacubitril+valsartan before ACE inhibitor therapy is initiated.
Duration of therapy	Indefinite
Important Drug Interactions	Concomitant use with **ACE inhibitors** is contraindicated. Concomitant use with **aliskiren** in patients with type 2 diabetes is contraindicated. Sacubitril+valsartan should not be co-administered with an **ARB**. Sacubitril+valsartan may increase the systemic exposure of **OATP1B1 and OATP1B3 substrates** such as **statins**, caution should be exercised upon co-administration with statins. Caution should be exercised when **sildenafil and other PDE-5 inhibitors** are initiated due to greater BP reductions compared to sacubitril+valsartan alone. Careful monitoring of serum **lithium** levels is recommended durng concomitant use with entresto. If a diuretic is used, the risk of lithium toxicity may be increased further. Concomitant use of **potassium-sparing diuretics** (e.g, triamterene, amiloride), **mineralocorticoid antagonists** (e.g. spironolactone, eplerenone), **potassium supplements**, or salt substitutes containing potassium may lead to increases in serum potassium, and to increases in serum creatinine. Monitoring of serum potassium is recommended if Entresto is co-administered with these agents Non-Steroidal Anti-Inflammatory Agents (**NSAIDs**) including selective cyclooxygenase-2 inhibitors (**COX-2 Inhibitors**): In elderly patients, volume-depleted patients (including those on diuretic therapy), or patients with compromised renal function, concomitant use of Entresto and NSAIDs may lead to an increased risk of worsening of renal function.
Administration instructions	Orally, BD dosing.

Monitoring requirements	Monitor blood pressure, renal function and potassium levels The main benefits of treatment relate to a reduction in CV mortality and first time HF hospitalisations, both components of the primary endpoint (composite) in the key clinical trial (PARADIGM-HF). A reduction in these events would be evidence of effectiveness.
Management of complications	Reduce dose or discontinue as appropriate
Basis of Protocol/Guideline: (including sources of evidence, references)	Entresto® Product Information. PBS PARADIGM-HF Study, McMurray et al, NEJM, Sep 2014.
Groups consulted in development of this guideline	Cardiac and Respiratory Clinical Stream

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GOVERNANCE	
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