Sacubitril/Valsartan Protocol to Support the Initiation And Up Titration for Heart Failure

Adapted with permission from NHS GGC

INTRODUCTION:

Sacubitril/valsartan (Entresto®) is indicated for the treatment of symptomatic heart failure with reduced ejection fraction (HFrEF). The NHS Ayrshire & Arran Formulary restricts use to initiation by the specialist heart failure multidisciplinary team in patients with:

- heart failure New York Heart Association (NYHA) class II to IV AND
- left ventricular ejection fraction (LVEF) ≤40% AND
- ongoing symptoms despite optimally tolerated treatment (e.g. beta blocker, ACEI inhibitor (ACEI) or Angiotensin Receptor Blocker (ARB) and either spironolactone or eplerenone).

PRE-INITIATION CHECKS:

- Undertake essential baseline investigations and checks (i.e. ECHO, BNP (or NT-proBNP) where available), symptom history, medication history, renal function tests, liver function tests, and blood pressure).
- Optimise ACEI/ARB, beta-blocker and either spironolactone or eplerenone as tolerated before considering initiation (Sacubitril/Valsartan can be considered in symptomatic patients hospitalised with heart failure as first line therapy, especially in non-ischaemic cardiomyopathy).

CONTRAINDICATIONS:

- Concomitant use of ACEI
- End-stage renal disease
- Known history of angioedema related to previous ACEI or ARB
- Hereditary or idiopathic angioedema
- Concomitant use with aliskiren*
- Severe hepatic impairment, biliary cirrhosis or cholestasis
- Pregnancy

*Note that aliskiren is not recommended by SMC for use in Scotland

See Summary of Product of Characteristics (available at www.medicines.org.uk) for full details.

CAUTIONS:

- Renal artery stenosis
- Hyperkalaemia (Treatment should not be initiated if the potassium level is >5.4 mmol/L)
- New York Heart Association Class IV
- Moderate hepatic impairment (Child-Pugh B classification or with AST/ALT values more than twice the upper limit of the normal range)

See Summary of Product of Characteristics (available at www.medicines.org.uk) for full details.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS:

- *Lithium*: this combination is not recommended; if it proves necessary, careful monitoring of serum lithium level is recommended
- *Atorvastatin:* sacubitril/valsartan can increase peak serum concentrations of atorvastatin by up to two fold and total exposure by up to 1.3 fold. Close monitoring of liver function tests and for myalgia is recommended and doses of atorvastatin may need to be reduced if problems are encountered.
- *Potassium salts*
- *Non-steroidal anti-inflammatory agents (NSAIDs)*

Please note: This is not an exhaustive list of potential clinically significant drug interactions. See the BNF (www.medicinescomplete.com) or Summary of Product Characteristics (www.medicines.org.uk) for further detail.

PHARMACEUTICAL ASPECTS:

- Sacubitril/valsartan is assumed to be suitable for administration in a weekly compliance box (Novartis have advised that tablets were found to be stable for at least 3 months in stability studies in so called 'open dish' conditions without any packaging).
- No data is available on whether tablets can be crushed or dispersed in water if needed. Therefore, this cannot be recommended and would be a clinical decision made on a case-by-case basis.

INITITATION PROCEDURES:

WASH-OUT PERIOD: If the patient is already prescribed an ACEI, the ACEI **MUST** be stopped 36 hours prior to initiation of sacubitril/valsartan to minimise the risk of angioedema. The importance of this wash-out period must **ALWAYS** be communicated directly to the patient, to the GP (in writing) and, if the person receives a weekly compliance aid, the community pharmacy (verbally, at the point the prescription is issued).

RECOMMENDED STARTING DOSES:

Previous Therapy	Additional Considerations Regarding Blood Pressure and Renal Function	Recommended Sacubitril/Valsartan Starting Dose
Patients tolerating medium to high dose ACEI or ARB before switch		
ACEI or ARB prior to initiation ≥50% ESC target dose	SBP >110mmHg **AND** eGFR>60 ml/min/1.73m^2	49/51mg twice daily*
ACEI or ARB prior to initiation ≥50% ESC target dose	SBP ≥100-110mmHg **AND/OR** eGFR ≥30-60 ml/min/1.73m^2	49/51mg twice daily* OR 24/26mg twice daily at clinician discretion
ACEI or ARB prior to initiation ≥50% ESC target dose	eGFR <30 ml/min/1.73m^2	No safety data in this population, so extreme caution needed. If cardiologist agrees that benefit outweighs the risks then start 24/26mg twice daily. Renal function and serum potassium should be monitored more frequently in this group.
ACEI or ARB prior to initiation ≥50% ESC target dose	SBP <100mmHg	Not routinely recommended (unlicensed use) and not covered by this guidance, although may be considered at the discretion of the heart failure specialist.
Patients tolerating low dose ACEI or ARB before switch		
ACEI or ARB prior to initiation <50% ESC target dose	SBP ≥100mmHg **AND** eGFR ≥30ml/min/1.73m^2	24/26mg twice daily
ACEI or ARB prior to initiation <50% ESC target dose	eGFR <30ml/min/1.73m^2	No safety data in this population, so extreme caution needed. If cardiologist agrees that benefit outweighs the risks then start 24/26mg twice daily. Renal function and serum potassium should be monitored more frequently in this group.
ACEI or ARB prior to initiation <50% ESC target dose	SBP <100mmHg	Not routinely recommended (unlicensed use) and not covered by this guidance, although may be considered at the discretion of the heart failure specialist.
Patients not taking ACEI or ARB prior to sacubitril/valsartan		
Not prescribed ACEI or ARB	Any SBPs and eGFR	Specialist/Hospital initiation

*Patients with AST/ALT more than twice normal reference range should be started on 24/26mg twice daily.

RECOMMENDED TITRATION SCHEDULE:

Patients starting on Lowest Dose of Sacubitril/Valsartan		
STEP 1. 24/26mg twice daily for four weeks*	STEP 2. 49/51mg twice daily for four weeks*	STEP 3. 97/103mg twice daily indefinitely
Patients starting on Middle Dose of Sacubitril/Valsartan		
	STEP 1. 49/51mg twice daily for four weeks*	STEP 2. 97/103mg twice daily indefinitely

*Prescribe in four weekly cycles to reduce wastage, unless pressing clinical reasons dictate otherwise. When uptitrating the dose DO NOT routinely tell patients to take two of the previous strength, as this introduces added risk and will be less cost effective if continued long-term. Use professional discretion where needed.

POST-INITIATION / UP-TITRATION CHECKS:

All patients started on sacubitril/valsartan should have blood pressure and renal function rechecked 7 to 14 days after initiation and 7 to 14 days after any up-titration. Follow up monitoring (i.e. renal function, blood pressure and tolerance) in all patients is recommended.

ONGOING PRESCRIBING AND MONITORING:

The patient's GP practice is able to continue to repeat prescribe in collaboration with the cardiac specialist according to this protocol. The GP practice will also undertake long-term follow-up monitoring (as per core annual GP practice care) after the patient is stabilised.

UNDESIRABLE EFFECTS AND PHARMACOVIGILANCE:

See Summary of Product of Characteristics (available at www.medicines.org.uk) for full details.

Problem	General Advice
Hyperkalaemia	
Serum potassium <5.5mmol/L	• No action needed
Serum potassium >5.5 and <6.0 mmol/L	• Confirm potassium concentration in a non-haemolysed sample • Reinforce low potassium diet and restriction of food/drinks with high potassium content (e.g orange juice, melon, bananas, low-salt substitutes etc) • Review other medical regimen (including dietary supplements, salt substitutes and over-the-counter medications) for agents known to cause hyperkalaemia and consider reduction in dose or discontinuation of these agents • Consider down-titration (e.g halving dose) or temporarily discontinue sacubitril/valsartan according to clinician judgement • Repeat serum potassium measurement after 2-3days • If serum potassium <5.5 mmol/L, consider resumption of sacubitril/valsartan at lower dose with repeat potassium within 7 days
Serum potassium ≥6.0 mmol/L	• Immediately discontinue sacubitril/valsartan • Confirm potassium concentration in a non-haemolysed sample • Urgently evaluate patient and treat hyperkalaemia as clinically indicated (refer to GP or hospital) • Apply all measures outlined for serum potassium >5.5 and <6.0 mmol/L above • Eventually if serum potassium <5.5 mmol/L, resumption of sacubitril/valsartan may be considered after individual case review by cardiologist
Worsening Renal Function	
eGFR decreases by <25% from baseline AND eGFR ≥30 ml/min/1.73m^2	• No action needed
eGFR decreases by ≥ 25-40% from baseline OR eGFR decreases to <30 ml/min/1.73m^2	• Check for potentially reversible causes of renal dysfunction such as NSAIDs (or other medications known to affect renal function), volume decrease or urinary infection • Consider down-titration (e.g. halving dose) or temporary discontinue sacubitril/valsartan according to clinician judgement then sacubitril/valsartan should be stopped • Repeat eGFR measurement after 5-7 days • When eGFR is only decreased by <25% from baseline AND eGFR ≥30 ml/min/1.73m^2, consider restarting sacubitril/valsartan at lower dose with repeat eGFR within 5-7 days
eGFR decreases by ≥ 40% from baseline	• If a patient eGFR decreases by ≥ 40% from baseline, clinicians will check for potentially reversible causes of renal dysfunction (see above) • If no other obvious potentially reversible causes of renal dysfunction are identified or according to clinician judgement then sacubitril /valsartan should be stopped • Repeat eGFR measurement after 5-7 days • Repeat eGFR at least weekly until levels return to acceptable values • Every effort should be made to restart sacubitril/valsartan but discuss all re-challenges with consultant before restarting
Symptomatic Hypotension	
Symptomatic Hypotension	• Correct any treatable cause (e.g. hypovolemia) • If hypotension persists, any antihypertensive drug and non-disease-modifying drugs, such as diuretics, calcium channel blockers (e.g. amlodipine), nitrates, and alpha-blockers, should be down-titrated or stopped first before down-titration of sacubitril/valsartan • If hypotension persists, sacubitril/valsartan should be down-titrated or even temporarily withdrawn according to clinical judgement
Angioedema-like Events (e.g. swelling around mouth, lips or eyes)	
Angioedema-like events	• Immediately and permanently discontinue sacubitril/valsartan • Discuss immediately with consultant medic to agree if treatments for angioedema-like event is needed • If this occurs, the allergy status should be updated in the patient's notes and the electronic systems in both primary and secondary care • A Yellow Card Report must be completed (www.mhra.gov/yellowcard)

Significant suspected reactions to sacubitril/valsartan should be reported to the Yellow Card Scheme www.mhra.gov.uk/yellowcard