BNSSG Shared Care Guidance
Please complete all sections

Section 1: Heading

Drug	Sacubitril/valsartan (Entresto ®)
Amber ***one month***	
Indication	Symptomatic chronic heart failure with reduced ejection fraction in adult patients. NICE TA 388 states it is recommended as an option for treating symptomatic chronic heart failure with reduced ejection fraction only in people: • with New York Heart Association (NYHA) class II to IV symptoms and • with a left ventricular ejection fraction of 35% or less and • who are already taking a stable dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor-blockers (ARBs)
Specialty / Department	Cardiology
Trusts	University Hospitals Bristol and Weston NHS Foundation Trust North Bristol NHS Trust

Section 2: Treatment Schedule

Usual dose and frequency of administration *(Please indicate if this is licensed or unlicensed and any relevant dosing information)*	• The recommended starting dose is 49mg/51mg twice daily, except in the situations described below. The dose should be doubled at 2-4 weeks to the target dose of one tablet of 97 mg/103 mg twice daily, as tolerated by the patient. • The majority of patients will have reached full titration/maximum optimised dose under the care of the HF team prior to a GP taking over prescribing. However, patients with renal impairment or low blood pressure may require one last titration within Primary Care as this will not have been possible during the one month period. In these cases, a clear plan will be documented in the clinic letter/ discharge information and Monday to Friday advice and guidance can be sought for further support if needed. • A starting dose of 24 mg/26 mg twice daily should be considered for patients with systolic blood pressure (SBP) 100 to 110 mmHg.
Route and formulation	Oral, tablets

Duration of treatment	Maintenance treatment, for as long as is tolerated/required under cardiologist instruction.

Section 3: Monitoring

Please give details of any tests that are required before or during treatment, including frequency, responsibilities (please state whether they will be undertaken in primary or secondary care), cause for adjustment and when it is required to refer back to the specialist.

Baseline tests - where appropriate

1. **Systolic blood pressure** - treatment should not be initiated unless SBP is >100 mmHg. (See section 2 for dose reduction information)
2. **Renal function** - no dose adjustment is required in patients with mild (Estimated Glomerular Filtration Rate [eGFR] 60-90 ml/min/1.73 m2) renal impairment. A starting dose of 24 mg/26 mg twice daily should be considered in patients with moderate renal impairment (eGFR 30-60 ml/min/1.73 m2). As there is very limited clinical experience in patients with severe renal impairment (eGFR <30 ml/min/1.73 m2) it should be used with caution and a starting dose of 24 mg/26 mg twice daily is recommended. There is no experience in patients with end-stage renal disease, hence use is not recommended in that cohort.
3. **Serum potassium** - treatment should not be initiated if the serum potassium level is >5.4 mmol/l. Monitoring of serum potassium is recommended, especially in patients who have risk factors such as renal impairment, diabetes mellitus or hypoaldosteronism or who are on a high potassium diet or on mineralocorticoid antagonists.
4. **Liver Function** - there is limited clinical experience in patients with moderate hepatic impairment (Child Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. Caution is therefore recommended in these patients. Recommended dose is 24mg/26mg twice daily.

Renal function and blood pressure should be checked within 2 weeks after initiating therapy

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Subsequent tests - where appropriate *(Please indicate who takes responsibility for taking bloods and interpreting results)*

Test	Frequency	Who by	Action/management
u/e and Blood pressure	1-2 weeks after dose change	Primary care	Advice from Heart failure specialist should be sought, and temporary down-titration or discontinuation considered if patients experience: • Clinically significant hyperkalaemia +/- 30% reduction in renal function. • Symptomatic hypotension during treatment.
u/e and blood pressure	At 1 month post stable dose then at 3 months and every 6 months thereafter	Primary care	
liver function test, fbc	Annually	Primary care	

Section 4: Side Effects

Please list only the most pertinent side effects and management. Please provide guidance on when the GP should refer back to the specialist. For everything else, please see BNF or SPC.

Side effects and management	Please refer to Summary of Product Characteristics (SPC) for full list of adverse effects. Most common side effects (see section 6 for management advice): • hyperkalaemia • hypotension • renal impairment • If patients experience tolerability issues (systolic blood pressure [SBP] ≤95 mmHg, symptomatic hypotension, hyperkalaemia > 5.4mmol/l, renal dysfunction), adjustment of concomitant medicinal products, temporary down-titration or discontinuation of sacubitril/valsartan is recommended.
Referral back to specialist	• If symptoms do not resolve after dose reduction, discontinue treatment and consult specialist at the next available opportunity. • If patient experiences angioedema (see section 6) discontinue immediately and refer to specialist.

Section 5: Other Issues

(e.g. Drug Interactions, Contra-indications, Cautions, Special Recommendations)

Please list only the most pertinent action for GP to take (For full list please see BNF or SPC)

Issues	Please refer to Summary of Product Characteristics (SPC) for full details. **Interactions resulting in a contraindication:** ACE inhibitors: • The concomitant inhibition of neprilysin and ACE may increase the risk of angioedema. • Sacubitril/valsartan must not be started for 2 days after taking the last dose of an ACE inhibitor. • An ACE inhibitor must not be started for 2 days after the last dose of sacubitril/valsartan. Aliskiren: • Aliskiren-containing products are contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2). • The combination of sacubitril/valsartan with direct renin inhibitors such as aliskiren is not recommended. **Interactions resulting in concomitant use not being recommended:** Sacubitril/valsartan contains valsartan, and therefore should not be co-administered with another ARB containing product. **Interactions requiring precautions:** OATP1B1 and OATP1B3 substrates e.g. statins: • Sacubitril/valsartan may increase the systemic exposure of OATP1B1 and OATP1B3 substrates such as statins. Caution should be exercised when co-administering sacubitril/valsartan with statins. Co-administration of Entresto increased the Cmax of atorvastatin and its metabolites by up to 2-fold and AUC by up to 1.3-fold in studies. Caution should therefore be exercised when co-administering Entresto with atorvastatin; a maximum dose of

	40mg daily is advised. If side effects are experienced, switch to simvastatin 40mg daily. PDE5 inhibitors including sildenafil: • Addition of a single dose of sildenafil to sacubitril/valsartan at steady state in patients with hypertension was associated with a significantly greater blood pressure reduction compared to administration of sacubitril/valsartan alone. Therefore, caution should be exercised when co-administering sildenafil or another PDE5 inhibitor with sacubitril/valsartan. Potassium: • Concomitant use of potassium-sparing diuretics (e.g. amiloride), mineralocorticoid antagonists (e.g. spironolactone, eplerenone), potassium supplements, salt substitutes containing potassium or other agents (such as heparin) may lead to increases in serum potassium and serum creatinine. Monitoring of serum potassium is recommended if sacubitril/valsartan is co-administered with these agents Non-steroidal anti-inflammatory agents (NSAIDs), including selective cyclooxygenase-2 (COX-2) inhibitors: • NSAIDS should be avoided in severe heart failure and alternative agents should be used where possible. • In the elderly, those who are volume- depleted (including those on diuretic therapy), or with compromised renal function, concomitant use of sacubitril/valsartan and NSAIDs may lead to an increased risk of worsening renal function. Monitoring of renal function is recommended in patients on sacubitril/valsartan who are takingNSAIDs concomitantly. Lithium: • Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or angiotensin II receptor antagonists. Interactions between sacubitril/valsartan and lithium have not been investigated. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased further. • Furosemide: • Co-administration of sacubitril/valsartan and furosemide reduced Cmax and AUC of furosemide by 50% and 28%, respectively. While there was no relevant change in urine volume, the urinary excretion of sodium was reduced within 4 hours and 24 hours after co-administration. OATP and MRP2 transporters: • The active metabolite of sacubitril and valsartan are OATP1B1, OATP1B3, OAT1 and OAT3 substrates. Valsartan is also a MRP2 substrate. Therefore, co-administration with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampicin, ciclosporin), OAT1 (e.g. tenofovir, cidofovir) or MRP2 (e.g. ritonavir) may increase the systemic exposure of sacubitril or valsartan. Appropriate care should be exercised when initiating or ending concomitant treatment with such medicinal products. Metformin: • Co-administration of sacubitril/valsartan with metformin reduced both Cmax and AUC of metformin by 23%. When initiating therapy with sacubitril/valsartan in patients receiving metformin, diabetes management should be monitored. **Sacubitril/valsartan is contra-indicated in the following patients:** 1. Hypersensitivity to the active substances or to any of the excipients

2. Concomitant use with ACE inhibitors. Sacubutril/valsartan must not be administered for 2 days after discontinuing ACE inhibitor therapy.
3. Known history of angioedema related to previous ACE inhibitor or ARB therapy.
4. Hereditary or idiopathic angioedema.
5. Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2).
6. Severe hepatic impairment, biliary cirrhosis and cholestasis.
7. Pregnancy; not recommended in the first trimester, contraindicated in second and third trimester. Not recommended during breast-feeding.

Sacubitril/ valsartan should be used in caution in the following situations:

Hypotension
Treatment should not be initiated unless SBP is >100 mmHg. Cases of symptomatic hypotension have been reported in patients treated with sacubitril/valsartan during clinical studies, especially in patients ≥65 years old, patients with renal disease and patients with low SBP (<112 mmHg)

When initiating therapy or during dose titration, blood pressure should be monitored routinely. If hypotension occurs, temporary down-titration or discontinuation of therapy is recommended. Dose adjustment of diuretics, concomitant antihypertensives and treatment of other causes of hypotension (e.g. hypovolaemia) should be considered

Symptomatic hypotension is more likely to occur if the patient has been volume-depleted, e.g. by diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Sodium and/or volume depletion should be corrected before starting treatment. Corrective action must be carefully weighed against the risk of volume overload.

Impaired renal function
See section 3

Evaluation of patients with heart failure should always include assessment of renal function. Patients with severe renal impairment may be at greatest risk of hypotension.

Worsening renal function
Treatment may be associated with decreased renal function. The risk may be further increased by dehydration or concomitant use of non-steroidal anti-inflammatory agents.

An increase in serum creatinine of < 30% / decrease in eGFR < 25% is acceptable.

[If serum creatinine rises by >15% but <30% from initial baseline continue but repeat U&Es in a further 1 to 2 weeks. If serum creatinine increases at any point ≥30% from initial baseline, review the patient including assessment of fluid status and blood pressure. Reduce concurrent diuretics if there is clinical evidence of hypovolaemia/over diuresis].

Hyperkalaemia
See section 3

	Treatment should not be initiated if the serum potassium level is >5.4 mmol/l. Use of sacubitril/valsartan may be associated with an increased risk of hyperkalaemia, although hypokalaemia may also occur. If patients experience clinically significant hyperkalaemia adjustment of concomitant medicinal products, or temporary down-titration or discontinuation is recommended. If serum potassium level is >5.4 mmol/l discontinuation should be considered. **Angioedema** Angioedema has been reported. If angioedema occurs, treatment should be immediately discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. It must not be re-administered. In cases of confirmed angioedema where swelling has been confined to the face and lips, the condition has generally resolved without treatment although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx likely to cause airway obstruction, appropriate therapy, e.g. adrenaline solution 1 mg/1 ml (0.3-0.5 ml), and/or measures necessary to ensure a patent airway, should be promptly administered. As they may be at higher risk for angioedema, caution is recommended if sacubitril/valsartan is used in patients with a prior history of angioedema. Sacubitril/valsartan is contraindicated in patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy or with hereditary or idiopathic angioedema. Black patients have an increased susceptibility to develop angioedema. **Patients with renal artery stenosis** Sacubitril/valsartan may increase blood urea and serum creatinine levels in patients with bilateral or unilateral renal artery stenosis. Caution is required in patients with renal artery stenosis and monitoring of renal function is recommended. **Patients with NYHA functional classification IV** Caution should be exercised in patients with NYHA functional classification IV due to limited clinical experience in this population. **Patients with hepatic impairment** See section 3 Sacubitril/valsartan is contraindicated in patients with severe hepatic impairment (Child-Pugh C classification), biliary cirrhosis or cholestasis.
Reminder to ask patient about specific problems	1. Ensure 2 day (48 hours) washout period if currently taking ACE inhibitor. There is no wash out period when switching from an ARB. 2. Discuss the need to omit therapy if 'sick' to avoid Acute Kidney Injury (AKI); and when to restart when recovered. (Significant diarrhoea/vomiting or unable to maintain oral intake for over 12 hours)

Section 6: Advice to the patient

Advice for prescribing clinician to inform patient

1. Patients should be advised to read the patient information leaflet
2. Tablets must be swallowed with a glass of water and may be taken with or without food. If a dose is missed, the patient should take the next dose at the scheduled time.
3. Patients should be informed of the common side effects and the need to inform the prescriber if they experience any side effects.
4. Pregnancy: Advise female patients of childbearing age about the consequences of exposure to sacubitril/valsartan during pregnancy. Discuss treatment options with women planning to become pregnant. Ask patients to report pregnancies to their clinician as soon as possible.
5. Advise patients to allow a 2 day wash-out period if switching from or to an ACE inhibitor. No wash-out period is necessary if switching from or to an ARB
6. If the patient is unwell and unable to maintain an adequate oral fluid intake for > 12 hrs or has severe diarrhoea/vomiting, sacubitril/valsartan should be omitted until clinically improved.
7. Treatment may occasionally cause drowsiness/fatigue, so advise caution if operating machinery/driving.

Section 7: Generic principles of shared care for SECONDARY CARE

Please do not amend.

Core responsibilities

1. Initiating treatment and prescribing for the first month
2. Undertaking the clinical assessment and monitoring for the first month.
3. Communicate details of the above in 1 and 2 to GP within the first month of treatment. This information should be transferred in a timely manner.
4. Refer patients to GP and provide information of further action where appropriate e.g. blood test is due.
5. To provide advice to primary care when appropriate.
6. Review concurrent medications for potential interaction prior to initiation of Sacubitril/valsartan.
7. Stopping treatment where appropriate or providing advice on when to stop.
8. Reporting adverse events to the MHRA.
9. Reminder to ask patients about particular problems see section 5.

Section 8: Generic principles of shared care for PRIMARY CARE

Please do not amend.

Core responsibilities

1. Responsible for taking over prescribing after the first month
2. Responsible for the clinical assessment and monitoring after the first month
3. Review of any new concurrent medications for potential interactions.
4. Reporting adverse events to the MHRA.
5. Refer for advice to specialist where appropriate.
6. Reminder to ask patients about particular problems see section 5.

Section 10: Contact Details

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Section 11: Document Details

Date prepared	May 2023
Prepared by	UHBW heart failure team/consultant cardiologists and Pharmacy Reviewed May 2018; D.Goddard, Y.Ismail, R.Brown.
Date approved by JFG	
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Section 12: Collaboration

All shared care protocols should be BNSSG wide where possible. Specialists in any one discipline are encouraged to collaborate across the health community in preparing shared care guidance. Please give details

1. Robert Brown, Cardiac Pharmacist, North Bristol NHS Trust
2. University Hospitals Bristol NHS Foundation Trust, Heart Failure Team

Section 13: References

Please list references

1. Sacubitril/Valsartan SmPC (Summary of Product Characteristics), updated October 2017:
2. https://www.medicines.org.uk/emc/product/7751 NICE TA388 - Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction, April 2016