This guideline provides prescribing and monitoring guidance for sacubitril valsartan therapy. It should be read in conjunction with the Summary of Product Characteristics (SPC) available on www.medicines.org.uk/emc and the BNF.

BACKGROUND FOR USE

Sacubitril valsartan is a nephrilysin inhibitor (sacubitril) with an angiotensin II receptor blocker (ARB; valsartan). It is licensed for treatment of symptomatic chronic heart failure with reduced ejection fraction in adults.

NICE TA 388 recommends sacubitril valsartan as an option for chronic heart failure patients who remain symptomatic despite optimal medical treatment. It is offered only in people:

- With New York Heart Association (NYHA) class II to IV symptoms AND
- With a left ventricular ejection fraction (LVEF) of 35% or less AND
- Who are already taking an optimised and stable dose of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blockers (ARB).

NICE TA 388 states that sacubitril valsartan must be initiated by a heart failure specialist with access to a multidisciplinary Heart Failure Team. An example checklist to support implementation of the drug can be found using the following link: https://www.nice.org.uk/guidance/ta388/resources/example-checklist-2551344448

In Buckinghamshire, the joint Formulary Management Group has approved the use of sacubitril valsartan in patients who have LVEF <35% and who are tolerating optimal medical therapy to include ACEI or ARB, beta blocker and either spironolactone or eplerenone who:

- Have had a recent unplanned heart failure admission without an obvious precipitating cause despite optimal medical therapy (OMT).
- Are at risk of unplanned hospital admission or who have worsening symptoms despite OMT, but who have a predicted good/stable prognosis.
- Patients who remain heavily symptomatic and at risk from unplanned admission despite OMT, i.e. NYHA III or IV.

In Buckinghamshire, treatment must be initiated by a consultant cardiologist or non-medical prescribers in the Heart Failure Team. Dose titration, monitoring and prescribing for the first three months must be by the Heart Failure Team. After the dose is stabilised the patient’s care will be transferred to the GP.

Evidence from PARADIGM-HF TRIAL (2014) demonstrated that patients with heart failure with reduced ejection fraction (LVEF <35%) and NYHA class II - IV treated with sacubitril valsartan versus standard of care (ACEI - enalapril) had reduced mortality risk and reduced risk of heart failure hospitalisation.

SUPPORTING INFORMATION

Contraindications

- Bilateral renal artery stenosis
- Aortic or mitral valve stenosis or obstructive cardiomyopathy
- Known hypersensitivity to sacubitril valsartan or any of the excipients
- History of angioedema of any cause (including previous ACEI or ARB treatment)
- Pregnancy
- Breastfeeding
- Serum potassium level >5.4 mmol/L
- Concomitant use with ACEI or ARB – sacubitril valsartan must NOT be started for at least 48 hours after discontinuing ACEI. This does not apply when stopping an ARB and starting sacubitril valsartan.
- Concomitant use with aliskiren in patients with diabetes mellitus.
- Severe hepatic impairment, biliary cirrhosis, cholestasis (Child-Pugh C classification).
- Treatment should not be initiated unless systolic blood pressure (SBP) is ≥100 mmHg.
- End stage renal disease.

Cautions

- Patients with a documented intolerance of ACEI due to symptomatic hypotension:
  - Consider re-challenging with a longer acting ACEI. Care if asymptomatic hypotension (systolic BP <100 mmHg).
- Patients on high dose diuretics (i.e. furosemide >80 mg daily):
  - Increased risk of hypotension and renal dysfunction.
- Moderate hepatic impairment (Child-Pugh B classification) or with aspartate aminotransferase (AST)/alanine aminotransferase (ALT) values more than twice the upper limit of normal.

Cautions for use are covered in ‘Dosage’, ‘Side effects and actions to be taken’ and ‘Notable Drug Interactions’ below. Valsartan in sacubitril valsartan is more bioavailable than in other marketed tablet formulations of valsartan.², ³

Dosage

Sacubitril valsartan must NOT be started for at least 48 hours after discontinuation of an ACEI due to the potential risk of angioedema. This does not apply when stopping an ARB and starting sacubitril valsartan and ARBs.

The recommended starting dose is:
- 50 mg (24 mg/26 mg) twice daily.
- Consider a starting dose of 100 mg (49 mg/51 mg) twice daily for patients on higher doses of ACEI or ARB (i.e. more than 50% of the maximum dose).
- The dose should be doubled every 2 - 4 weeks to the target of 200 mg (97 mg/103 mg) twice daily, as tolerated by the patient.

If a dose is missed, the tablet should be taken at the next scheduled time.

Tablets should be swallowed whole with water and can be taken with or without food.

Dose in renal impairment

<table>
<thead>
<tr>
<th>Mild (eGFR 60 - 90 ml/min)</th>
<th>No dose adjustment required.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate (eGFR 30 - 60 ml/min)</td>
<td>Consider starting dose of 50 mg (24 mg/26 mg) twice daily.</td>
</tr>
<tr>
<td>Severe (eGFR &lt;30 ml/min)</td>
<td>Limited clinical experience. Use with caution. Starting dose of 50 mg (24 mg/26 mg) twice daily is recommended.</td>
</tr>
<tr>
<td>End stage renal disease</td>
<td>No experience. Use of sacubitril valsartan is not recommended.</td>
</tr>
</tbody>
</table>

Time to response

7 to 10 days

RESPONSIBILITIES

Specialist: Cardiology Consultant and Heart Failure Team

1. Assess the patient. Establish the diagnosis and assess the patient’s ability to concord with treatment.
2. Ensure a 48 hour washout period for patients taking ACEIs. Ensure the patient understands that an ACEI, ARB or aliskiren should not be taken with sacubitril valsartan.
3. Undertake pre-treatment assessment (see below).
4. Prescribe sacubitril valsartan for the first month and review the patient within 2 to 4 weeks of initiation of sacubitril valsartan.
5. Undertake the ongoing monitoring schedule (see below) and dose adjustments.
6. Ensure a prescription is provided for any dose change. Prescribing will be managed in secondary care for the first 3 months. During this time, prescriptions of sacubitril valsartan may
be prescribed by cardiology consultants, specialist cardiology registrars or non-medical prescribers in the Heart Failure Team.
7. Any dose adjustments, clinical concerns or discontinuation of treatment will be communicated to Cardiology (verbally or through patient notes) and to the GP (by email or letter).
8. Prior to completion of the 3 months under specialist care, and once the patient is stable, the specialist will request that the patient should be transferred to the GP for ongoing monitoring and prescribing of sacubitril valsartan from 3 months. The transfer of care will be communicated to the GP by email or letter and will include prescribing information. The GP must be informed and given at least 2 weeks’ notice for when they will need to take over prescribing.
9. The Heart Failure Team will be available for verbal advice to the GP if the patient’s condition changes or deteriorates. Following this advice GPs may refer patients back to the Heart Failure Team for assessment if this is required. See Referral Form in Appendix A.
10. The Heart Failure Team will ensure the patient and carer(s) are given information regarding the treatment and a contact for the Heart Failure Team if they have any concerns.
11. Any adverse events must be reported to the Medicines Healthcare Regulatory Agency (MHRA) using the yellow card scheme.

Patient counselling conducted by specialist but reinforced by the GP

- Explain the expected benefits of treatment to the patient:
  - Treatment can improve their symptoms, prevent their heart failure getting worse, increase survival and decrease hospital admissions.
- Symptoms may not improve immediately. It may take a few weeks or months to have a full effect.
- Advise patients:
  - Report adverse effects, e.g. hypotension or dizziness.
  - Take the first dose at night as they may experience a first dose hypotensive effect.
  - Renal function monitoring is needed.
  - Avoid non-steroidal anti-inflammatory drugs (NSAIDs) bought over the counter, soluble tablets and salt substitutes high in potassium (K+).
  - If a dose is missed, the tablet should be taken at the next scheduled time.

GP
1. Sacubitril valsartan must not be given with ACEI, ARB or aliskiren. Therefore remove ACEI, ARB or aliskiren from the patient’s medication list on the electronic medical record.
2. Prescribe sacubitril valsartan in accordance with the amber initiation guideline, i.e. at the dose recommended by the Heart Failure Team (3 months after treatment is initiated). This includes non-urgent prescribing dose adjustments recommended by the Heart Failure Team following a request from the GP for advice or rapid referral.
3. Undertake annual monitoring (see Ongoing Monitoring Schedule below).
4. Refer to the Heart Failure Team for advice when necessary.

Hospital Pharmacy: Duration of Supply
After initiation, a total of 3 months treatment will be provided by secondary care. Thereafter it is expected that the GP will continue prescribing.

PRE-TREATMENT ASSESSMENT (by the specialist)

- Blood chemistry (serum creatinine, urea, potassium, sodium and estimated glomerular filtration rate (eGFR))
- Echocardiogram demonstrating LVEF <35% within the last 12 months
- Medication review (including optimisation of heart failure medication)
- Electrocardiogram (ECG) and resting heart rate
- Blood pressure (BP)
- Weight
ONGOING MONITORING SCHEDULE
The following parameters will be monitored 2 - 4 weeks after initiation and at each dose adjustment:

- Pulse
- BP
- Blood chemistry (serum creatinine, urea, potassium, sodium and eGFR)

The specialist will undertake this monitoring from month 1 to 3 inclusive; the GP will undertake monitoring from month 4 onwards, including 12 monthly reviews.

SIDE EFFECTS AND ACTIONS TO BE TAKEN
The most commonly reported adverse reactions during treatment with sacubitril valsartan are hypotension, hyperkalaemia and renal impairment. For other side effects see SPC.

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angioedema and hypersensitivity</td>
<td>Stop sacubitril valsartan and monitor 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.</td>
</tr>
<tr>
<td>Hyperkalaemia serum K+ &gt;5.4 mmol/L</td>
<td>• Consider stopping sacubitril valsartan.*&lt;br&gt;• Consider stopping concomitant medication that can increase serum potassium (e.g. potassium-sparing diuretics (spironolactone, eplerenone, triamterene, amiloride), mineralocorticoid antagonists, potassium supplements).</td>
</tr>
<tr>
<td>Asymptomatic low BP (systolic blood pressure (SBP) &lt;100 mmHg)</td>
<td>Does not usually warrant a change in therapy, but BP requires monitoring and watch for worsening renal function.</td>
</tr>
<tr>
<td>Symptomatic hypotension (including dizziness, headache, syncope) (e.g. SBP &lt;100 mmHg)</td>
<td>• Monitor BP, consider ambulatory monitoring if available.&lt;br&gt;• Consider dose adjustment of concomitant antihypertensives.&lt;br&gt;• Consider treating other causes of hypotension (e.g. hypovolaemia).&lt;br&gt;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 with sacubitril valsartan; however, such corrective action must be carefully weighed against the risk of volume overload.&lt;br&gt;• Consider temporary down-titration or discontinuation of sacubitril valsartan.*</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>If eGFR &lt;60 ml/min consider:&lt;br&gt;• Stopping concomitant nephrotoxic medication (e.g. NSAIDs, diuretics).&lt;br&gt;• Dose reduction of sacubitril valsartan.&lt;br&gt;• Stopping sacubitril valsartan* (rarely needed unless GFR &lt;30).</td>
</tr>
<tr>
<td>Persistent dry cough</td>
<td>Review aetiology of cough, e.g. due to smoking, worsening heart failure/pulmonary oedema, respiratory disease.&lt;br&gt;• Review cough tolerability versus benefits of sacubitril valsartan.&lt;br&gt;• May require discontinuation of treatment. ARB alone may be tolerated.</td>
</tr>
<tr>
<td>Anaemia, hypoglycaemia, vertigo, fatigue, asthenia, gastro-intestinal disorders (diarrhoea, nausea, gastritis)</td>
<td>• Consider seeking specialist advice.</td>
</tr>
</tbody>
</table>

*Allow 48 hour wash out period before restarting an ACE inhibitor
NOTABLE DRUG INTERACTIONS (REFER TO BNF AND SPC for further information)

The following drugs are contraindicated with sacubitril valsartan:
- ACEI
- Aliskiren
- ARB

The risk of worsening renal function and heart failure is increased by concomitant use of NSAIDs and sacubitril valsartan.

The manufacturers’ state that caution is needed in patients taking statins as use of sacubitril valsartan may increase the systemic exposure to metabolites. No formal recommendations exist on management of the combination however sensible precautions would include patients being reminded to report symptoms such as muscle pains and jaundice.

Lithium and sacubitril valsartan has not been tested and is therefore 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.

Potassium supplements and potassium sparing diuretics may increase the risk of hyperkalaemia and potassium should be monitored.

Sacubitril valsartan taken with sildenafil is associated with significantly greater blood pressure reduction compared to administration of sacubitril valsartan alone. Therefore, caution should be exercised when sildenafil or another PDE5 inhibitor is initiated in patients treated with sacubitril valsartan.

Co-administration of sacubitril valsartan with rifampicin, ciclosporin, tenofovir, cidofovir, ritonavir may increase sacubitril valsartan levels.

Co-administration of sacubitril valsartan with metformin reduces the bioavailability of metformin by 23%. The clinical relevance of these findings is unknown. Therefore, when initiating therapy with sacubitril valsartan in patients receiving metformin, the control of the patient’s diabetes may need to be re-evaluated.

BACK-UP INFORMATION/ADVICE

<table>
<thead>
<tr>
<th>Contact Details</th>
<th>Wycombe and Amersham</th>
<th>Stoke Mandeville</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buckinghamshire Heart Failure Specialist Team</td>
<td>01494 426919 (8am – 4pm) On-call cardiologist registrar via switchboard (out-of-hours)</td>
<td></td>
</tr>
<tr>
<td>Medicines Resource Centre</td>
<td>01494 425355</td>
<td></td>
</tr>
<tr>
<td>Switchboard</td>
<td>01494 526161 (WH)</td>
<td>01296 315000</td>
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REFERENCES

1. NICE TA 388 ‘Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction’ available at: [https://www.nice.org.uk/guidance/TA388/chapter/1-recommendations](https://www.nice.org.uk/guidance/TA388/chapter/1-recommendations).
<table>
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<th>Sacubitril Valsartan for Symptomatic Chronic Heart Failure with Reduced Ejection Fraction - Amber Initiation Guideline</th>
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<tbody>
<tr>
<td><strong>Guideline Number</strong></td>
<td>817FM</td>
</tr>
<tr>
<td><strong>Version</strong></td>
<td>2</td>
</tr>
<tr>
<td><strong>Effective Date</strong></td>
<td>August 2020</td>
</tr>
<tr>
<td><strong>Review Date</strong></td>
<td>August 2023</td>
</tr>
<tr>
<td><strong>Original Version Published</strong></td>
<td>December 2016</td>
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<tr>
<td><strong>Approvals:</strong></td>
<td></td>
</tr>
<tr>
<td>Medicines Check (Pharmacy)</td>
<td>9th March 2020</td>
</tr>
<tr>
<td>Clinical Guidelines Group</td>
<td>18th August 2020</td>
</tr>
</tbody>
</table>
| **Original Author/s**  | Dr Piers Clifford, Consultant Cardiologist  
                        Kavan Nagi, Lead Pharmacist Cardiology  
                        Tracey Apps, Heart Failure Nurse  
                        Maire Stapleton, Formulary Manager  
                        Sarah Crotty, Bucks CCGs Head of Interface (Pharmacist) |
| **Reviewed by**        | Dr Piers Clifford, Consultant Cardiologist  
                        Kavan Nagi, Lead Pharmacist Cardiology  
                        Andrea Hollister, Medicines Optimisation Lead (Bucks CCG)  
                        Roshni Kotecha, Medicines Optimisation Pharmacist (Bucks CCG) |
| **SDU(s)/Department(s) responsible for updating the guideline** | Cardiology |
| **Uploaded to the Intranet** | 28th August 2020                                                                                       |

Buckinghamshire Healthcare NHS Trust/Buckinghamshire Clinical Commissioning Group
### Appendix A: Referral Form

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<thead>
<tr>
<th>Patient name:</th>
<th>Surname:</th>
<th>GP Name:</th>
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<tr>
<th>Address:</th>
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<thead>
<tr>
<th>Tel no:</th>
<th>DOB:</th>
<th>NHS no:</th>
<th>Tel no:</th>
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<tr>
<th>Referred by (details):</th>
<th>Referral reason/diagnosis:</th>
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<thead>
<tr>
<th>Tel no:</th>
<th>Date of referral:</th>
<th>Is this patient able to travel to a community/hospital clinic:</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Yes / No</td>
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### Past Medical History: Please attach copies of the following:

- [ ] GP summary of active problems
- [ ] GP summary of past medical history
- [ ] Summary of current medication
- [ ] Most recent ECHO
- [ ] Most recent U&Es
- [ ] Most recent ECG

### Contact:
Heart Failure Specialist Nursing Service Administrator  
Level 2 Tower Block  
Wycombe Hospital  
Queen Alexandra Road  
High Wycombe  
Bucks  
HP11 2TT  
Tel: 01494 426919  
E-Mail: buc-tr.CommHF@nhs.net

### Other risk stratification information required for referral  
**PLEASE CIRCLE:**
- NYHA Class: I  II  III  IV
- Medicines management issues
- Recent hospital admissions (<4 weeks)
- Hyponatraemia
- Chronic kidney disease (CKD) stage IV
- Raised WCC +/- CRP
- Orthopnoea/paroxysmal nocturnal dyspnea (PND)
- Dizziness
- Symptomatic arrhythmia