Hertfordshire and West Essex Integrated Care System

NHS Hertfordshire and West Essex Integrated Care Board

Sacubitril Valsartan (Entresto®) for Treating Symptomatic Chronic Heart Failure with Reduced Ejection Fraction

PRESCRIBING CRITERIA:

In line with NICE TA388, sacubitril valsartan 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 (LVEF) of 35% or less **and**
- who are already taking a stable dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor-blockers (ARBs)

Sacubitril valsartan may be considered for initiation by a heart failure specialist (i.e. consultant or specialist nurse/pharmacist) with access to a multidisciplinary heart failure team in the community or secondary care cardiology/heart failure clinic setting. The initiating specialist is responsible for ensuring the patient is stabilised on sacubitril valsartan and providing any necessary follow up.

Sacubitril valsartan must only be initiated after up-titration to maximum tolerated doses of combination standard therapy (ACE inhibitors [or ARBs if ACE inhibitor not tolerated], beta blockers and aldosterone antagonists) have failed to control symptoms. There is an expectation that prior to initiation, patients are on optimal combination standard therapy for a minimum of 3 months.

Heart Failure Specialist (Consultant or Specialist Nurse/Pharmacist)

Patient newly referred to secondary care or the community heart failure team or already on active caseload.
Baseline investigations (U&E's, BP, LFTs and FBC) completed.
Patient meets sacubitril valsartan prescribing criteria

- Initiated within secondary care with community heart failure team support
- Initiated or continued treatment by community heart failure team
- Initiated within secondary care with NO community heart failure team support

INITIAL MANAGEMENT

- Review the patient at 2-4 week intervals and undertake appropriate dose titration.
- Monitor renal function and blood pressure after each dose titration.
- Prescriptions to be issued by the specialist until the patient is stabilised on the maximum tolerated dose for at least one month.

- Stop currently prescribed ACE inhibitors or ARBs (ACEi therapy to be stopped by specialist 36 hours before starting sacubitril valsartan).
- Initiate, dose titrate and prescribe sacubitril valsartan generically.
- Provide counselling to the patient to improve adherence and manage any early adverse effects.
- Advise the patient to read the patient information leaflet inside the pack when they receive the medication.
- Inform the patient's GP at initiation of therapy. The correspondence (email or letter) should include clinical details such as the LVEF, NYHA class, recent blood test results and blood pressure. State in clear terms do not prescribe with ACE inhibitors or ARBs.

Primary Care

TRANSFER OF CARE

- Specialist provides GP with the baseline investigations and monitoring results, rationale of treatment choice, dose to be prescribed and any other information deemed necessary to ensure safe transfer of prescribing responsibility.
- GP takes over prescribing responsibility and review of treatment ensuring monitoring of: renal function; blood pressure; adverse effects including hyperkalaemia; and full blood count at least every 6 months throughout therapy.

Problems in Primary Care

- Discontinue treatment immediately if angioedema occurs and seek further advice from the specialist team.
- Seek advice and discuss management plan with the specialist team if concerns arise about adherence, tolerability issues and/or contra-indications, monitoring results, adverse drug events or if the patient's clinical condition has changes.

Sacubitril Valsartan (Entresto®) has been licensed (SmPC) and approved by NICE for the treatment of symptomatic chronic heart failure with reduced ejection fraction NICE TA388 (April 2016).
NICE Chronic Heart Failure Guidelines (Sept 2018).

Prescribing Support Document

Prescribing of sacubitril valsartan (Entresto®) for treating symptomatic chronic heart failure with reduced ejection fraction is to be initiated by a heart failure specialist (i.e. consultant or specialist nurse/pharmacist) with access to a multidisciplinary heart failure team in the community or secondary care cardiology/heart failure clinic setting. Prescribing will be maintained by the specialists until the patient is stabilised on the maximum tolerated dose for at least one month. Following this period, prescribing and monitoring will be transferred to primary care.

The aim of this prescribing support document is to ensure sufficient information is provided to enable GPs to be confident to take on the clinical and legal responsibility for prescribing sacubitril valsartan (Entresto®) in stable patients.

BACKGROUND AND INDICATION(S) FOR USE

Sacubitril valsartan (Entresto®) is an angiotensin receptor neprilysin inhibitor, including both a neprilysin inhibitor (sacubitril) and an angiotensin II receptor blocker (ARB; valsartan). It is licensed for use in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.[1]

SUPPORTING INFORMATION

Criteria for patient selection in line with ICB recommendations

NICE TA388 states that sacubitril valsartan 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 (LVEF) of 35% or less **and**
- who are already taking a stable dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor-blockers (ARBs).[2]

Sacubitril valsartan must only be initiated after up-titration to maximum tolerated doses of combination standard therapy (ACE inhibitors [or ARBs if ACE inhibitor not tolerated], beta blockers and aldosterone antagonists) have failed to control symptoms. There is an expectation that prior to initiation, patients are on optimal combination standard therapy for a minimum of 3 months.[3]

RESPONSIBILITIES

Specialist Responsibilities - Consultant/Specialist nurse/independent prescribing pharmacist	
1	Confirm patient adherence with combination standard therapy prior to considering sacubitril valsartan
2	Assess the clinical need and suitability of the patient for sacubitril valsartan and ensure recommendation is in line with ICB recommendations and criteria recommended in NICE TA388
3	Complete baseline investigations (as outlined in monitoring section) and ensure that currently prescribed ACE inhibitor or ARBs are stopped. (ACE inhibitor therapy to be stopped at least 36 hours before starting sacubitril valsartan)
4	Initiate, dose titrate and prescribe sacubitril valsartan until the patient is stabilised on the maximum tolerated dose for at least one month. Ensure patient is on the correct starting dose based on systolic blood pressure, renal function and hepatic function
5	Prescribe sacubitril valsartan using the generic name to reduce risk of concomitant prescribing of ACE inhibitor or additional ARB therapy
6	Inform the GP at initiation of therapy. The correspondence (email or letter) should include clinical details such as the LVEF, NYHA class, recent blood test results and blood pressure. State in clear terms do not prescribe with ACE inhibitors or ARBs
7	Ensure the patient/carer has agreed to treatment and has been counselled at initiation. Advise the patient to read the patient information leaflet inside the pack when they receive the medication
8	Following initiation, review the patient at 2-4 week intervals and undertake appropriate dose titration
9	Once the patient is stabilised on the maximum tolerated dose for at least one month, provide the GP with the baseline investigations and monitoring results, rationale of treatment choice, dose to be prescribed and any other information deemed necessary to ensure safe transfer of prescribing responsibility for the patient to the GP
10	Be available for advice to the GP if the patient's clinical condition changes, if there are concerns about adherence, if any test results indicate an abnormal result or when further advice is sought on monitoring, adverse events or down/up-titration or discontinuation
11	Continue to review the patient as part of the overall heart failure management/service and inform the GP of any suggested changes in prescribed therapy

Trust Pharmacist Responsibilities where prescribed by secondary care	
1	Screen the prescription and ensure patient is on correct dose based on systolic blood pressure, renal function and hepatic function
2	Ensure ACE inhibitor or ARBs are stopped. (ACE inhibitor therapy to be stopped at least 36 hours before starting sacubitril valsartan)
3	Counsel the patient

General Practitioner Responsibilities	
1	Prescribe sacubitril valsartan at the dose specified by the specialist service, using the generic name to reduce risk of concomitant prescribing of ACE inhibitor or ARB

2	Do not co-prescribe ACE inhibitors or ARB and ensure all (automatic) repeat prescriptions for such drugs are stopped
3	Provide monitoring as outlined in the monitoring section, referring to the specialist team where appropriate
4	Discontinue treatment immediately if angioedema occurs and seek further advice from the specialist service
5	Seek advice and discuss management plan with the specialist team if concerns arise about adherence, tolerability issues and/or contra-indications, monitoring results, adverse drug events or if the patient's clinical condition has changed
6	Monitor adherence with therapy and raise concerns with the specialist team as required

CONTRAINDICATIONS AND PRECAUTIONS

- Treatment should not be initiated in patients with serum potassium level >5.4 mmol/l or in those with systolic blood pressure (SBP) <100 mmHg
- Sacubitril valsartan should not be co-administered with an ACE inhibitor or an ARB due to increased risk of angioedema
  - Sacubitril valsartan must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with sacubitril valsartan is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of sacubitril valsartan
  - Sacubitril valsartan contains valsartan, and therefore should not be co-administered with another ARB containing product
- Hypersensitivity to the active substances or to any of the excipients
- Known history of angioedema related to previous ACE inhibitor or ARB therapy
- Hereditary or idiopathic angioedema
- Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m^2)
- End-stage renal disease (eGFR < 15 ml/min/1.73 m^2)
- Severe hepatic impairment, biliary cirrhosis and cholestasis (Child-Pugh C)
- Second and third trimester of pregnancy and/or breastfeeding[(1)]

CAUTIONS

- Renal impairment – eGFR between 15 and 60 ml/min/1.73 m^2 (see recommended dose adjustments below). **NB**: Patients with eGFR < 30 ml/min/1.73 m^2 are at greater risk of hypotension.
- Moderate hepatic impairment (Child-Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range (see recommended dose adjustments below).
- Prior history of angioedema (contraindicated if related to previous ACE inhibitor or ARB therapy)
- Renal artery stenosis
- NYHA class IV – limited evidence of use
- Drug interactions (see notable drug interactions section below)[(1)]

DOSAGE AND TITRATION

- **Treatment should not be initiated in patients with serum potassium level >5.4 mmol/l or with SBP <100 mmHg**
- The recommended starting dose of sacubitril valsartan is one tablet of 49 mg/51 mg twice daily. 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.
- A starting dose of 24 mg/26 mg twice daily should be considered for patients with SBP ≥100 to 110 mmHg.

Dosage and titration in renal impairment

eGFR > 60 ml/min/1.73 m^2	No dose adjustment required
eGFR 30-60 ml/min/1.73 m^2	Recommended starting at a dose of: **24 mg/26 mg TWICE daily**
eGFR 15-29 ml/min/1.73 m^2	Limited clinical experience Use with caution, starting at a dose of: **24 mg/26 mg TWICE daily**
eGFR < 15 ml/min/1.73 m^2 (end-stage renal disease)	There is no experience in this patient group. Use of sacubitril valsartan is not recommended.

Dosage and titration in hepatic impairment

- No dose adjustment is required when administering sacubitril valsartan to patients with mild hepatic impairment (Child-Pugh A classification).
- 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. Sacubitril valsartan should be used with caution in these patients and the recommended starting dose is 24 mg/26 mg twice daily.
- Sacubitril valsartan is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification) [1]

NB: Valsartan contained within Entresto® is more bioavailable than the valsartan in other marketed tablet formulations;26 mg, 51 mg, and 103 mg of valsartan in Entresto® is equivalent to 40 mg, 80 mg and 160 mg of valsartan in other marketed tablet formulations, respectively.[1]

PRE-TREATMENT ASSESSMENT BY THE SPECIALIST AND ONGOING MONITORING SCHEDULE

Monitoring at initiation and dose titration (SPECIALIST)	**Monitoring stable patients (GP)**
• U&E's, BP, LFTs and FBC at initiation	• U&E's, BP and FBC at least every 6 months
• U&Es and BP after each dose titration (every 2 to 4 weeks)	

All patients with chronic heart failure require monitoring in line with NICE NG106, Chronic heart failure in adults: diagnosis and management. More detailed monitoring will be needed if the patient has significant comorbidity or if their condition has deteriorated since the previous review. The frequency of monitoring should depend on the clinical status and stability of the patient. The monitoring interval should be short (days to 2 weeks) if the clinical condition or medication has changed, but is needed at least 6-monthly for stable patients with proven heart failure.[4]

SIDE EFFECTS AND ACTIONS TO BE TAKEN

The most commonly reported adverse reactions for sacubitril valsartan are hypotension, hyperkalaemia and renal impairment. For a detailed list of side effects, please refer to the summary of product characteristics (SmPC)

Considerations for temporary down titration and discontinuation (tolerability issues)

Adjustment of concomitant medicinal products, temporary down titration or discontinuation may be required if the patient experiences tolerability issues whilst on treatment. These include:

- SBP ≤ 95mmHg
- Symptomatic hypotension
- Hyperkalaemia (serum potassium > 5.4mmol/l)
- Renal dysfunction

Seek advice and discuss management plan with the specialist heart failure team if any of the above tolerability issues occur.

Angioedema has been reported in patients treated with sacubitril valsartan with a higher incidence in people of African family origin. If angioedema occurs, sacubitril valsartan should be **immediately discontinued** and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. Sacubitril valsartan must not be re-administered. If sacubitril valsartan is discontinued by a primary care clinician, further advice should be sought from the specialist heart failure team regarding the patient's management plan.

NOTABLE DRUG INTERACTIONS (for a comprehensive list, please see BNF or SmPC)

Drug / Drug class	Recommendation
ACE-inhibitors	• Avoid concurrent use and allow a washout period of 36 hours when switching between ACE-I and sacubitril valsartan treatment due to the risk of angioedema.
ARBs	• Avoid prescribing any additional ARBs as sacubitril valsartan already contains the ARB valsartan.
Aliskiren	• Avoid concurrent use due to a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function.
Potassium-sparing diuretics, mineralocorticoid antagonists, potassium supplements or salt substitutes, or any agent that increases potassium	• Monitoring of serum potassium is recommended.
Statins	• Sacubitril valsartan can increase the plasma concentration of atorvastatin and its metabolites. Caution should be exercised when co-administering statins.
Phosphodiesterase type 5 (PDE5) inhibitors e.g. sildenafil, tadalafil, vardenafil	• Concomitant use can result in a significant reduction in blood pressure after a single dose. Caution should be exercised if a PDE5 inhibitor is initiated.
Nitrates e.g. nitroglycerine	• Co-administration with a nitrate was associated with a reduction in heart rate by 5bpm. In general, no dose adjustment is required.
Non-steroidal anti-inflammatory drugs (NSAIDs) including cyclo-oxygenase-2 (COX-2) inhibitors)	• Concomitant use can worsen renal function; therefore, if use of sacubitril valsartan and an NSAID is required, close monitoring of renal function is advised.
Lithium	• ACE-I and ARB are known to cause reversible increases in lithium levels and toxicity, therefore the concomitant use of sacubitril valsartan and lithium is not recommended. Monitor lithium levels carefully if the combination is necessary.
Metformin	• Sacubitril valsartan can reduce the plasma concentration of metformin - the clinical status of patients receiving metformin should be monitored.
Metabolic interaction	• Caution should be exercised with the co-administration of sacubitril valsartan with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampicin, ciclosporin), OAT1 (e.g. tenofovir, cidofovir) or MRP2 (e.g. ritonavir), as these may increase levels of the sacubitril active metabolite or of valsartan.

(Table copied and adjusted from 'Sacubitril Valsartan for the treatment of symptomatic chronic heart failure with reduced ejection fraction – prescribing guidance' written by South East London Area Prescribing Committee 12.03.2019) [5]

VERSION CONTROL

Version	Change details	Authors	Date
V1.0	Shared care protocol	Saskia Vercaeren (Senior pharmaceutical advisor, Pharmacy and Medicines Optimisation Team East and North Herts CCG) Krupa Mandalia (Pharmacist Advanced, Cardiology stroke and Elderly care, East and North Herts NHS Trust)	Content agreed PCMMG ENHCCG April 2018 Approved TPC ENHT April 2018, ratified July 2018
V2.0	Document amended to prescribing support document. - No changes to clinical content - Reference to shared care arrangements removed		February 2021, Approved TPC ENHT 04/2021 Approved PCMMG ENHCC 06/2021
V3.0	Harmonisation of West Essex pathway, East & North Hertfordshire prescribing support document and HMMC (Herts Valleys only) decision document.	Jamil Khakoo (Medicines Optimisation Pharmacist, HWE ICB). Mihir Varia (Lead Pharmaceutical Adviser - Clinical Effectiveness, HWE ICB) Jessica Peplow (Clinical Lead Specialist for Heart Failure and Cardiac Rehabilitation, CLCH)	Hertfordshire & West Essex Area Prescribing Committee, December 2022

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1. Summary of product characteristics Sacubitril valsartan (Entresto®) film-coated tablets, http://www.medicines.org.uk/emc/, Accessed: 27/7/2022
2. Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction. Technology appraisal guidance (TA388), Published date: 27 April 2016, https://www.nice.org.uk/guidance/ta388, Accessed: 27/7/2022
3. Hertfordshire Medicines Management Committee, NICE TA 388 – Sacubitril-valsartan for treating symptomatic chronic heart failure with reduced ejection fraction, April 2016, https://hertsvalleysccg.nhs.uk/download_file/1153/389, Accessed 27/7/2022
4. Chronic heart failure in adults: diagnosis and management. NICE guideline (NG106), Published date: September 2018, https://www.nice.org.uk/guidance/ng106, Accessed 27/7/2022
5. Sacubitril valsartan for the treatment of symptomatic chronic heart failure with reduced ejection fraction – prescribing guidance, http://slcn.nhs.uk/wp-content/uploads/2019/10/hf-sacubitril-valsartan-hfref-prescribing-guidance-032019.pdf, Accessed 27/7/2022