Guy's and St Thomas' NHS Foundation Trust

Clinical Guideline

Sacubitril Valsartan for the treatment of symptomatic chronic heart failure with reduced ejection fraction – prescribing guidance

This is an external document and owned by the South East London Area prescribing committee. The document can be accessed here or via the South East London Area Prescribing Committee website.

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Prescribing SACUBITRIL VALSARTAN for the treatment of symptomatic chronic heart failure with reduced ejection fraction

This guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer

Sacubitril valsartan▼ (Entresto®) is a combination drug, including both a neprilysin inhibitor (sacubitril) and an angiotensin II receptor blocker (ARB; valsartan). It is licensed and approved by the National Institute for Health and Care Excellence (NICE) for the treatment of symptomatic chronic heart failure (HF) with reduced ejection fraction.

In South London, sacubitril valsartan may be considered for initiation by Heart Failure (HF) specialists for treating chronic HF in patients meeting all of the following criteria:

1. New York Heart Association (NYHA) class II to IV symptoms
2. On a stable dose of angiotensin-converting enzyme inhibitors (ACE-I) or an ARB
3. Left ventricular ejection fraction of 35% or less

Additional resources have been developed to support implementation including:

- Screening checklist and Notification of initiation of sacubitril valsartan used in the treatment of symptomatic chronic HF with reduced ejection fraction. This document **must be completed and sent to the General Practitioner (GP) on initiation.**
- Transfer of prescribing responsibility to primary care for sacubitril valsartan. . This document **must be completed and sent to the GP when transferring the prescribing responsibility** in accordance to South London guidelines.

Initiation of sacubitril valsartan should be undertaken by **Heart Failure specialists** with access to a multidisciplinary HF team. The initiating clinician is responsible for ensuring the patient is stabilised on sacubitril valsartan and providing any necessary follow up. During this time, efforts should be made to reinforce adherence and address any adverse effects.

Transfer of Prescribing Responsibility to Patient's Own GP

Prescribing responsibility to patient's own GP may be considered following **at least 3 months of treatment and when the patient has been stable on the maximum tolerated dose for at least one month**. The agreed transfer of prescribing responsibility form should be completed and forwarded to the GP. If sacubitril valsartan is prescribed for non-approved or unlicensed indications, prescribing responsibility will remain with the initiating clinician/organisation.

Contraindications (for details – see BNF or SPC)	**Cautions** (for details – see BNF or SPC)
• Hypersensitivity to the active substances or to any of the excipients • **Concomitant use with an ACE-I**. Sacubitril valsartan must not be administered until 36 hours after discontinuing ACE-I therapy and if sacubitril valsartan is to be stopped, an ACE-I must not be initiated until 36 hours after discontinuation of sacubitril valsartan therapy. • **Concomitant use with another ARB**, as the combination drug contains valsartan • Known history of angioedema related to previous ACE-I or ARB therapy • Hereditary or idiopathic angioedema • Systolic blood pressure (SBP) <100mmHg • End-stage renal disease • Serum potassium >5.4 mmol/L • Severe hepatic impairment, biliary cirrhosis and cholestasis (Child-Pugh C) • Concomitant use with aliskiren in patients with diabetes mellitus. Also avoid concomitant use with aliskiren in patients with renal impairment (estimated Glomerular Filtration Rate **(**eGFR) <60ml/min/1.73 m^2) • Pregnancy and/ or breastfeeding • For contra-indications for use with other medicines see overleaf	• Serum potassium levels >5mmol/l. Note: contraindicated if >5.4mmol/l • Renal artery stenosis • Renal impairment - eGFR 15-60ml/min/1.73m^2. NB: Patients with eGFR <30ml/min/1.73m^2 are at greater risk of hypotension • Moderate hepatic impairment (Child-Pugh B) or with alanine transaminase (ALT) / aspartate aminotransferase (AST) values more than twice the upper limit of the normal range • Dehydration • NYHA class IV – limited evidence of use • Drug interactions – see below

Note: BNF=British National Formulary; SPC=Summary of Product Characteristics

ON INITIATION OF SACUBITRIL VALSARTAN, ACEI or ARB therapy MUST BE DISCONTINUED
Sacubitril valsartan should be prescribed using the generic name to avoid concomitant prescribing of ACE-I or additional ARB therapy
ACE-I therapy must be discontinued at least 36 hours before initiation of sacubitril valsartan

Dosing

The recommended starting dose is one tablet of 49mg/51mg TWICE daily to be taken with water, with or after

food. The dose should be doubled at 2 to 4 week intervals to a maximum target dose of 97mg/103mg TWICE daily, or highest tolerated dose by the patient. This will be undertaken by HF specialist team.

A **reduced** starting dose of 24mg/26mg TWICE daily with a slow dose titration (doubling every 3 to 4 weeks) should be considered for patients with:

- Systolic blood pressure between 100 to 110mmHg.
- Moderate renal impairment (eGFR 30-60ml/min/1.73m^2). Note patient with severe renal impairment (eGFR <30ml/min/1.73m^2), sacubitril valsartan should be used with caution due to very limited experience and are also at greater risk of hypotension.
- Moderate liver impairment (Child-Pugh B classification or with AST/ALT greater than twice the upper limit of normal range) used with caution due to limited clinical experience.

Monitoring

Monitoring should be undertaken prior to initiation, and also before and after each dose titration. Blood pressure, renal function, serum potassium and adherence to medication should be checked at least six monthly with an annual review of liver function and a full blood count. More frequent monitoring should be undertaken if clinically indicated or in accordance with advice from the heart failure team.

Side effects (for full details see BNF or SPC)

- Most common reported adverse reactions for sacubitril valsartan were:
  a) **Hypotension** (reported in 17.6% of patients in PARADIGM-HF). It is recommended to review and correct volume and/ or salt depletion prior to starting treatment, if hypotension occurs during treatment, review patients' medication and consider adjusting those that are contributing to low blood pressure or review the dose of sacubitril valsartan which may need to be reduced or discontinued.
  b) **Hyperkalaemia** (reported in 11.6% of patients in PARADIGM-HF). Serum potassium should be monitored periodically especially in high risk patients (e.g. renal impairment, diabetes, hypoaldosteronism or patients receiving medicines that increase potassium). Dose reduction should be considered where the potassium level is 5.0mmol/L or greater. If potassium level is >5.4mmol/L then discontinue therapy and seek further advice from the HF team.
  c) Renal impairment (reported in 10% of patients in PARADIGM-HF). Renal function should be closely monitored and may need to dose adjust or discontinue sacubitril valsartan as indicated. Note: safety monitoring criteria in PARADIGM-HF excluded patients if eGFR declined by more than 35% within 2 weeks after initiation.
- Other common side effects include: anaemia, hypokalaemia, cough, nausea, diarrhoea and gastritis.
- Angioedema (reported in 0.5% of patients in PARADIGM-HF). Sacubitril valsartan should be discontinued if angioedema occurs and patient given the appropriate therapy and monitored for airway compromise.

Sacubitril Valsartan *is a black triangle drug - any adverse effect must be reported to the MHRA using the yellow card system and via the local incident reporting system*

Drug Interactions (for full details on drug interactions – see BNF or SPC)

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	• Concomitant use can worsen renal function; therefore, if use of sacubitril

(NSAIDs) including cyclo-oxygenase-2 (COX-2) inhibitors	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
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

Roles and Responsibilities

Initiating clinician / organisation	Patient's own GP
• To initiate sacubitril valsartan in line with NICE and local guidance • To provide counselling to improve adherence and address any early adverse effects • To ensure the patient's GP is informed about the cessation of ACE-I/ARB therapy • To supply sacubitril valsartan for the first 3 months of treatment and until a maximum tolerated stable dose is achieved for at least one month • Transfer of care to GP in line with local transfer of care guidance and give clear guidance of further follow-up required	• To ensure use of sacubitril valsartan is in line with NICE and local guidance • To agree to take over prescribing responsibility when the patient is stable on therapy (in line with the transfer of care guidance) • To emphasise the importance of adherence to sacubitril valsartan therapy and address any patient concerns • To ensure BP, renal monitoring, serum potassium and adherence are undertaken at least 6-monthly throughout therapy (with an annual review of liver function and a full blood count). Also review treatment in line with contra-indications, cautions and monitoring sections. If appropriate, seek specialist advice from heart failure team

References

1. NICE TA388 Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction. April 2016. Accessed 28th April 2016 at: https://www.nice.org.uk/guidance/ta388/resources/sacubitril-valsartan-for-treating-symptomatic-chronic-heart-failure-with-reduced-ejection-fraction-82602856425157
2. SPC Entresto. Novartis 5th Feb 2016. Accessed 8th April 2016 https://www.medicines.org.uk/emc/medicine/31244