Sacubitril Valsartan (Entresto®▼) – Amber, specialist initiated including dose titration to a stable dose

Criteria for use

- NICE TA388 recommends sacubitril valsartan 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 (or reported as moderate to severe) AND
  - who are already taking a stable and optimised dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor-blockers (ARBs)

Treatment with sacubitril valsartan should be started by a heart failure specialist with access to a multidisciplinary heart failure team. ALWAYS PRESCRIBE GENERICALLY

Local Swindon Pathway for access

- NICE recommend this drug is best suited to be initiated and titrated in a community heart failure clinic, where they can select the most suitable patients and monitor them closely for side-effects and titrate the dose accordingly
- Once stable, the patient can then be sent out to the GP for them to continue to prescribe

Treating Chronic Heart Failure due to Left Ventricular Systolic Dysfunction

First Line Treatment

Optimised ACE/ARB and Beta-blocker unless c/l

Optimisation done by:
- GWH Heart Failure Team (Consultant/Nurse)
- Community Heart Failure Team (Nurse led)
- GPs

Second Line Treatment

Refer for Specialist advice for options which include:
- Aldosterone antagonist – can be prescribed by GP with careful monitoring of electrolytes
- Combination ACE/ARB – can be prescribed by GP with careful monitoring of electrolytes
- Hydralazine in combination with nitrates to be prescribed by Specialist
- Sacubitril/valsartan – to be prescribed by Specialist

Swindon
- Diagnosis by echocardiogram
- Use agreed BNP pathway to ensure appropriate echo referral

Optimal doses of formulary and licensed ACE/ARB and beta blockers

<table>
<thead>
<tr>
<th>Type</th>
<th>Brand Name</th>
<th>Dose</th>
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</thead>
<tbody>
<tr>
<td>ACE-1</td>
<td>Rempril/ Lisinopril/ Perindopril</td>
<td>10mg daily (2 divided doses) 35mg od 4mg od</td>
</tr>
<tr>
<td>ARB</td>
<td>Losartan</td>
<td>150mg od 32mg od</td>
</tr>
<tr>
<td>ARB</td>
<td>Candesartan</td>
<td>160mg od</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>Bisoprolol/ Carvedilol</td>
<td>10mg od 25mg bid (50mg bid if wt &gt; 85kg)</td>
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</table>

- GPs should not initiate this drug themselves (unless they have a specialist interest in heart failure).

Important Drug Information

Sacubitril/valsartan must not be used concurrently with ACE inhibitors due to the risk of life threatening angioedema. It should also not be used with ARBs due to its angiotensin II receptor blocking activity

- Sacubitril/valsartan is a fixed dose combination preparation containing a first-in-class: Angiotensin Receptor Antagonist Neprilysin inhibitor (ARNi). It is a complex of valsartan and sacubitril
- Sacubitril is a black triangle drug, please monitor for and report any side effects through the yellow card reporting system www.mhra.gov.uk/yellowcard
- For GP - once Sacubitril/Valsartan has been started, please ensure that the previous ACE-I or ARB that the patient was on is REMOVED from their repeat medication list, ensure there is no electronic “live” prescriptions on the prescribing system and inform the community pharmacist.
Sacubitril Valsartan for Heart Failure

Dose Information (PRESCRIBE GENERICALLY)

- For full drug information please refer to the Summary of Product Characteristics [https://www.medicines.org.uk/emc/medicine/31244](https://www.medicines.org.uk/emc/medicine/31244)
- STOP the ACE-I that the patient was on for at least 36 hours before starting sacubitril/valsartan. (In practice, a more pragmatic 2 days washout will be used but the SPC stipulates at least 36 hours). A washout period is not needed if switching from an ARB to Sacubitril/valsartan.
- The recommended starting dose is Sacubitril 49mg/valsartan 51mg bd with or without food
- The dose should be doubled every 2-4 weeks to the target dose of Sacubitril 97mg/valsartan 103mg (200mg) bd as tolerated by the patient
- U&Es should be checked prior to initiation and before each dose titration
- Patients should have been titrated up to maximum tolerated doses of ACE-I or ARBs before trying Sacubitril/Valsartan.
- If systolic blood pressure between 100-110mmHg or moderate renal impairment (eGFR 30-60 ml/min/1.73m²) consider starting with lowest dose (24/26mg)

Further information on use in renal and hepatic impairment, adverse effects and drug interactions

- Drug interactions of note (not exhaustive) : (see SPC for full details)
  - Statins, PDE5-inhibitors, Rifampicin, ciclosporin and anti-virals, Metformin, Lithium, NSAIDS, Cox-2 inhibitors
- Contraindications (not exhaustive):
  - Do not use with Aliskiren
  - Patients with a known history of angioedema related to previous ACE-I or ARB therapy
  - SBP is less than 100mmHg
  - Renal and Hepatic impairment - no dose adjustment required in mild or moderate (eGFR 30-90mls/min/1.73m²) renal impairment or mild hepatic impairment.
  - Caution is recommended when using Sacubitril/valsartan in severe renal impairment or end stage renal disease or moderate hepatic impairment; use a starting dose of Sacubitril 24mg/valsartan 26mg bd.
  - Overall the adverse effect profile including the incidence of hypotension and associated adverse effects, particularly the propensity for Sacubitril/valsartan to precipitate renal impairment (due to decreased renal perfusion) is unclear from the available trial data
  - Side effects listed as very common (≥ 1/10) in the SPC are hyperkalaemia, hypotension and renal impairment
  - Careful upward titration may be needed to ensure patient tolerability and safety which in turn may lead to a decrease in overall efficacy and mortality. A lower strength is licensed to facilitate a lower initial dose and upward titration.

Tolerability

- If patients experience tolerability issues such as those listed below, dose adjustment of concomitant medications (e.g. diuretics/beta-blockers), temporary down-titration or discontinuation of Sacubitril/valsartan may be required. If further advice is needed, see contact details below.
  - Systolic blood pressure ≤95mmHg
  - Symptomatic hypotension
  - Hyperkalaemia (If above 5.4mmol/l consider dis-continuation)
  - Renal dysfunction
  - Symptomatic hypotension and decreased renal function is more likely to occur if the patient has been volume depleted, eg. By diuretic therapy, concomitant NSAID use, dietary salt restriction, diarrhoea or vomiting.
  - If a patient has tolerability problems after previously tolerating it then seek further advice on management.

Cost Information

- Sacubitril 24mg/valsartan 26mg 56 tabs: £91.56 Dose: 1 bd
- Sacubitril 49mg/valsartan 51mg 56 tabs: £91.56 Dose: 1 bd
- Sacubitril 97mg/valsartan 103mg 56 tabs: £91.56 Dose: 1 bd
- Due to the flat pricing structure, it is important that prescribers ensure dose optimisation to minimise cost (e.g. 1 tablet rather than 2)
- The cost of treating one patient with sacubitril/valsartan for one year = £1,098 vs £13- £41 for enalapril 10-20 mg bd

Other Information

- The number needed to treat, to prevent one primary event and one death was 21 and 32 respectively (from Paradigm HF trial)
- There is limited data beyond 27 months. The long term efficacy and safety profile of Sacubitril/valsartan has not been defined. There is also limited data in patients aged less than 18 years and patients over 75 years of age
- There is limited comparative data with alternative treatments for heart failure
- Improvement in quality of life measures have not been adequately assessed to date
- There is limited clinical experience with use of Sacubitril/valsartan in NYHA class IV patients. Hence this should be used with caution in such patients.

Contact details of local services

- Heartfunctionteam@nhs.net or Community Heart Failure Team, Mercury Ward Office, GWH

Medicines Management Team Swindon CCG, The Pierre Simonet Building, North Swindon Gateway, North Lathan Road, Swindon, SN25 4DL, Tel: 01793 683700, SWICCG.medsop@nhs.net