SACUBITRIL/VALSARTAN film-coated tablets (Entresto® ▼)

The Pan Mersey Area Prescribing Committee recommends the prescribing of SACUBITRIL/VALSARTAN film-coated tablets (Entresto® ▼) for treating symptomatic chronic heart failure following specialist initiation and in accordance with NICE TA388

AMBER following specialist initiation

NICE TA388[1] (April 2016) 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
  AND
- who are already taking a stable 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 (as defined below in local implementation recommendations) with access to a multidisciplinary heart failure team. Dose titration and monitoring should be performed by the most appropriate team member as defined in NICE NG106[2]: Chronic heart failure in adults: diagnosis and management (September 2018).

Patients being considered for sacubitril/valsartan treatment should have been on optimal* first line heart failure therapy for a minimum of 3 months - this should include an optimised and stable dose of ACE inhibitor or ARB.

**Optimal first line therapy is defined as beta blocker, mineralocorticoid receptor antagonist and ACE inhibitor or ARB, titrated to maximum tolerated dose.*

Further information on when sacubitril/valsartan treatment may be considered, is available in the updated NICE Pathway: Treating chronic heart failure with reduced ejection fraction

Prescribing and monitoring of sacubitril/valsartan must be retained by the heart failure team during dose titration and until the patient is stabilised on the optimum dose.

See full Implementation Notes for further details of recommendations for safe local implementation.

Note: Patients who are not eligible for treatment under this statement may be considered on an individual basis where their GP or consultant believes exceptional circumstances exist that warrant deviation from the rule of this policy. In this situation, follow locally defined processes.

SUPPORTING INFORMATION

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Effectiveness [1,3]

Entresto® is a single molecule product containing sacubitril valsartan sodium salt complex, not a combination product. It exhibits the mechanism of action of an angiotensin receptor neprilysin inhibitor by simultaneously inhibiting neprilysin (via sacubitril) and by blocking the angiotensin II type-1 receptor (via valsartan).

The pivotal trial, PARADIGM-HF, compared sacubitril valsartan (n=4187) with enalapril (n=4212), both given in combination with standard care, including beta-blockers and aldosterone antagonists.

Sacubitril/valsartan was statistically significantly more effective at reducing hospital admissions and improving both overall mortality and cardiovascular (CV) mortality.

NICE concluded that sacubutril/valsartan would be considered cost-effective use of NHS resources, with a plausible ICER at the upper end of the acceptable range.

Safety [4]

The most commonly reported adverse effects are: hypotension, hyperkalaemia and renal impairment. Angioedema was also reported.

Contraindications

- concomitant use with ACE inhibitors or ARBs
- concomitant use with aliskiren in patients with diabetes or eGFR less than 60ml/min/1.73m^2
- severe hepatic impairment, biliary cirrhosis or cholestasis
- hereditary or idiopathic angioedema, or known history of angioedema related to previous ACE inhibitor/ARB therapy
- pregnancy

Cautions

Co-administration with statins, PDE-5 inhibitors, NSAIDs/COX-2 inhibitors, lithium, potassium-sparing or containing products (see also Drug Safety update (Feb 16) – risk of severe hyperkalaemia with spironolactone and ARBs).

See SPC for full details of all contraindications, cautions and interactions.

Cost

There is a flat pricing structure for sacubitril/valsartan. Annual cost to treat one patient (excl. VAT) = £1,193. [5]

NICE estimates the cost of implementing this guidance at an additional £25,000 per 100,000 population in 2016/17, rising to £138,000 per 100,000 by 2020/21. [6]

There may be a small offset due to potential reduction in hospital admissions.

More detailed local costings were produced by the North West Coast Strategic Clinical Network & Senate when the NICE TA was published, and distributed to the relevant local CCGs.

Patient factors [4]

- Patients should be given a sacubitril/valsartan patient alert card when starting treatment.
- Treatment should not be initiated in patients with serum potassium level >5.4mmol/L or with systolic blood pressure (BP) <100mmHg.
- No dose adjustment required in mild renal or mild hepatic impairment.
- Not recommended in end-stage renal disease.
- Caution in patients with renal artery stenosis.

See SPC for full details of recommended dose adjustments in moderate-to-severe renal impairment and moderate hepatic impairment.

Prescribing information [1,4,7]

> **STOP ACE INHIBITOR OR ARB 48 HOURS BEFORE COMMENCING SACUBITRIL/VALSARTAN TREATMENT**

> Initiation and titration of sacubitril/valsartan should be undertaken by the specialist heart failure team.

> The recommended starting dose is sacubitril 49mg/valsartan 51mg twice daily (reduced to sacubitril 24mg/valsartan 26mg twice daily in patients previously taking low doses of ACE inhibitor/ARB, moderate-to-severe renal impairment, moderate hepatic impairment, or systolic BP 100-110mmHg).

> The dose should be doubled every 2 to 4 weeks to the recommended target dose of sacubitril 97mg/valsartan 103mg twice daily, as tolerated by the patient. If patients experience tolerability issues (systolic BP ≤95mmHg, symptomatic hypotension, hyperkalaemia, renal dysfunction), adjustment of concomitant medication, temporary down-titration or discontinuation of sacubitril/valsartan is recommended.

> Tablets should be swallowed with a glass of water and can be taken with or without food.

> Monitoring for sacubitril/valsartan is the same as for ACE inhibitors/ARBs (i.e. U&E and blood pressure after every dose change and once yearly when stable).

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Local implementation recommendations [1,4,7]

Within the Pan Mersey health economy, the term 'specialist' is understood to be a Consultant Cardiologist, or a Cardiology GPSi, with experience of treating chronic heart failure and who has access to a specialist multidisciplinary heart failure team.

- The North West Coast Strategic Clinical Network has issued a position statement on the use of sacubitril/valsartan and a treatment algorithm that describes the local access routes to treatment.
- The following patients should not be considered for sacubitril/valsartan treatment:[7]
  - ACE inhibitor/ARB naïve
  - Serum potassium >5.4mmol/L
  - End stage renal disease
  - Systolic BP <100mmHg
  - ARB intolerant (if ACE intolerant, try ARB first)
  - LVEF > 35%
  - eGFR < 30mL/min
  - Severe hepatic impairment
- Patients being considered for sacubitril/valsartan treatment should be symptomatic, with a LVEF of 35% or less, and have been on optimal* first line heart failure therapy for a minimum of 3 months – this should include an optimised and stable dose of ACE inhibitor or ARB.
  **Optimal first line therapy is defined as beta blocker, mineralocorticoid receptor antagonist and ACE inhibitor or ARB, titrated to maximum tolerated dose.*
- The specialist must initiate treatment. This includes issuing the first prescription for sacubitril/ valsartan and ensuring arrangements are in place for the patient to receive an alert card.
- ACE inhibitor or ARB treatment **must** be stopped 48 hours before commencing sacubitril/valsartan treatment.
- The specialist must provide adequate patient information and ensure that the patient understands when to stop their ACE inhibitor or ARB treatment and when to start taking sacubitril/valsartan. This information should be clearly communicated in a timely manner (e.g. within 1 week) to the patient's GP and preferably also to the community pharmacist.
- A template patient information leaflet and GP communication letter have been produced by the North West Coast Strategic Clinical Networks. Specialists initiating therapy must use these to ensure clear, consistent and adequate communication.
- The GP should ensure that the ACE inhibitor or ARB is discontinued from the patient's repeat prescription and clearly record that the patient is receiving sacubitril/valsartan, as a hospital prescribed medicine, in the patient's Summary Care Record.
- Following initiation by the specialist, dose titration, monitoring and patient review may be undertaken by a specialist heart failure nurse. However, prescribing and monitoring of sacubitril/valsartan must be retained by the heart failure team during dose titration and until the patient is stabilised on the maximum tolerated dose. This is expected to be a minimum of 3 months of prescribing by the heart failure team to allow dose titration and review of the patient once they are stable on optimum dose.
- Once the patient is considered stable on optimum dose, the patient's GP will normally be requested to take on the ongoing prescribing of sacubitril/valsartan, following clear written communication from the heart failure team (including a list of all current heart failure medications and doses). The patient must receive an adequate further supply of sacubitril/valsartan from the heart failure team to allow the safe transfer of prescribing to primary care.
- The ongoing dose of sacubitril/valsartan must be communicated clearly to the patient's GP. To avoid confusion, always use the standard dose format from the SPC and GP clinical systems:
  - Sacubitril 24mg/valsartan 26mg
  - Sacubitril 49mg/valsartan 51mg
  - Sacubitril 97mg/valsartan 103mg
- **Do not** prescribe the dose as 50mg, 100mg or 200mg.
- **Do not** prescribe by brand name or use in communication between healthcare professionals. The routine use of generic sacubitril/valsartan is an additional safety prompt to prescribers that the patient is receiving a valsartan-containing treatment and therefore must not be prescribed concomitant ACE inhibitor or ARB.

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References

1. National Institute for Health and Care Excellence. NICE TA388 (April 2016): Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction. Accessed 06 Nov 2018 at: https://www.nice.org.uk/guidance/ta388
2. National Institute for Health and Care Excellence NICE NG106 Chronic Heart Failure in Adults: Diagnosis and management (September 2018). Accessed 06 Nov 2018 at: https://www.nice.org.uk/guidance/ng106
3. McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993-1004.
4. Novartis Pharmaceuticals UK Ltd. Summary of Product Characteristics - Entresto film-coated tablets; 26 July 2018. Accessed 06 Nov 2018 at: http://www.medicines.org.uk/emc/medicine/31244
5. NHS Business Services Authority. dm+d browser. Accessed 08 January 2019 at: https://apps.nhsbsa.nhs.uk/DMDBrowser/DMDBrowser.do
6. National Institute for Health and Care Excellence. Resource impact template: Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction (TA388); April 2016. Accessed 06 Nov 2018 at: https://www.nice.org.uk/guidance/ta388/resources
7. North West Coast Strategic Clinical Networks. Statement on the use of Sacubitril/Valsartan (Entresto®) for the treatment of symptomatic chronic heart failure with reduced ejection fraction; June 2016. Accessed 06 Nov 2018 at: https://www.england.nhs.uk/north/north-west-coast-strategic-clinical-networks/about-us/cvd-and-stroke-protocols/