What is it?
Sacubitril/Valsartan is an angiotensin receptor neprilysin inhibitor, including both a neprilysin inhibitor (Sacubitril) and an angiotensin II receptor blocker (Valsartan).

NICE Guidance
NICE TA388: Sacubitril/Valsartan is recommended by NICE as a therapy for symptomatic chronic heart failure with reduced ejection fraction, in patients with:

- New York Heart Association (NYHA) class II to IV symptoms
- Left ventricular ejection fraction ≤35%
- Taking a stable dose of Angiotensin Converting Enzyme (ACE) inhibitor or Angiotensin II Receptor Blocker (ARB).

Treatment with Sacubitril/Valsartan should be started by a heart failure specialist 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 CG108 - Chronic Heart Failure in Adults: Management.

When will GPs be asked to prescribe?
GPs will only be asked to prescribe Sacubitril/Valsartan after specialist initiation is complete. Sacubitril/Valsartan will be started by a Consultant Cardiologist. The process of specialist initiation will last for a minimum of six weeks, during which time patients will be reviewed and the dose of Sacubitril/Valsartan will be increased to the maximum tolerated dose.

Preparations available
Sacubitril/Valsartan 24mg/26mg film-coated tablets (Entresto®)
Sacubitril/Valsartan 49mg/51mg film-coated tablets (Entresto®)
Sacubitril/Valsartan 97mg/103mg film-coated tablets (Entresto®)

Dosage and Administration
Sacubitril/Valsartan should not be co-administered with an ACE inhibitor or an ARB.

Due to the potential risk of angioedema when used concomitantly with an ACE inhibitor, Sacubitril/Valsartan must not be started for until at least 36 hours have elapsed after discontinuing ACE inhibitor therapy. The valsartan contained within Entresto® is more bioavailable than the valsartan in other marketed tablet formulations

- Patients will be asked to stop their ACE inhibitor or ARB at least 36 hours prior to starting Sacubitril/Valsartan (48hrs may be more practical).
Table 1. Suggested dose recommendations and patient criteria

<table>
<thead>
<tr>
<th>Normal starting dose</th>
<th>49 mg/51 mg twice daily</th>
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<tr>
<td>Low starting dose in patients with any of the following:</td>
<td>24 mg/26 mg twice daily</td>
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<tr>
<td>Patients currently taking low ACEI/ARB dose (Enalapril ≤10 mg daily, Lisinopril ≤10 mg daily, Ramipril ≤5 mg daily, Valsartan ≤160 mg daily, Losartan ≤50 mg daily, Candesartan ≤16 mg daily)</td>
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<tr>
<td>Systolic BP ≥100 to 110 mmHg</td>
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<tr>
<td>Estimated GFR 30-60 ml/min/1.73 m²</td>
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<tr>
<td>Elderly (age &gt;65 years)</td>
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<tr>
<td>Moderate hepatic impairment (Child-Pugh B) or AST/ALT &gt;2 x upper limit of normal range</td>
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Dose Escalation
Increase by doubling of dose every 2–4 weeks (depending on starting dose) until a target dose of 97 mg/103 mg twice daily is reached, or to the limit of tolerability (if lower). Check blood pressure and renal function at 1–2 weeks after each dose escalation.

Start: The drug is initiated by the heart failure clinic at either low or normal dose of one tablet twice a day depending on the above criteria. Due to the potential risk of angioedema when used concomitantly with an ACE inhibitor, it must not be started for at least 36 hours after discontinuing ACE inhibitor therapy. The valsartan contained within Entresto® is more bioavailable than the valsartan in other marketed tablet formulations. A 2-week supply of medication will be provided from the hospital. A letter will be sent to GP and a copy will be handed to patient.

- After two weeks: Specialist clinic review. Check blood pressure and renal function. Increase dose of Sacubitril/Valsartan if medication has been well tolerated with no symptomatic hypotension and no deterioration in renal function. A 2 to 4-week supply of medication will be provided from the hospital.

- Four or six weeks: Specialist clinic review. Check blood pressure and renal function. Continue maintenance dose or increase dose if medication has been well tolerated with no symptomatic hypotension and no deterioration in renal function. Prescribe a further 2-week supply from the hospital. A letter will be sent to the GP, informing them of the maintenance dose, with a request to continue prescribing.

Sacubitril/Valsartan can be taken with or without food. The film-coated tablet should be swallowed whole with water. If a dose is missed, the patient should take the next dose at the scheduled time.

Dose Modifications
See Table 1 for suggested starting dose recommendations: Prescribe one tablet of 24mg/26mg strength as a starting dose if the patient has previously tolerated only low dose ACE inhibitor/ARB, and/or the patient is aged over 65 years; then increase to one tablet of 49mg/51mg strength after 2 weeks following the same criteria as outlined above.

Renal Impairment
- Mild eGFR 60–90 ml/min/1.73 m²: No dose adjustment is required.
- Moderate eGFR 30–60 ml/min/1.73 m²: Starting dose is one tablet of 24mg/26mg strength twice a day.
- Severe eGFR <30 ml/min/1.73 m²: This was an exclusion criteria in the PARADIGM-HF trial.
Hepatic Impairment

- Mild: No dose adjustment is recommended
- Moderate (Child-Pugh B or AST/ALT values > 2x upper limit of normal): Starting dose is one tablet of 24mg/26mg strength twice a day.
- Severe (Child-Pugh C classification, biliary cirrhosis or cholestasis): Contraindicated

INFORMATION FOR PRESCRIBING

Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed (refer to Summary of Product Characteristics - SPC)
- Concomitant use of ACE inhibitors
- Angioedema related to previous ACE inhibitor or ARB therapy; hereditary or idiopathic angioedema
- Patients with severe hepatic impairment, biliary cirrhosis or cholestasis
- Patients with end stage renal failure
- Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 min/min/1.73m²)
- Pregnant or breastfeeding patient

Cautions

- Hypotension. Treatment should not be initiated unless SBP is ≥100 mmHg. Monitor blood pressure when initiating therapy and during dose titration. If symptomatic hypotension occurs, temporary down-titration or discontinuation is recommended - see SPC for further information
- Hyperkalaemia. Treatment should not be initiated in patients with serum potassium level >5.4 mmol/L. If patients experience clinically significant hyperkalaemia, adjustment of concomitant medicinal products, or temporary down–titration or discontinuation is recommended. If serum potassium level is >5.4 mmol/L, discontinuation should be considered
- Renal artery stenosis: monitoring of renal function is recommended
- NYHA IV symptoms: limited clinical experience in this population
- Moderate hepatic impairment (Child-Pugh B or AST/ALT values > 2x ULN): limited clinic experience in this population – see dose modifications above.

What are the main side-effects?
The most commonly reported adverse reactions (>10% of patients) with Sacubitril/Valsartan are hypotension, hyperkalaemia and renal impairment. Reported adverse events are generally in line with that reported for other medicinal products acting on the renin angiotensin-aldosterone system. Angioedema has been reported in 0.5% of patients. If this occurs treatment must be immediately discontinued, appropriate therapy and monitoring provided until complete and sustained resolution of symptoms has occurred.

Drug Interactions

- ACE Inhibitor or Aliskiren - Do not take with Sacubitril/Valsartan (Entresto®).
- ARBs - Entresto® contains valsartan, and therefore should not be co-administered with another ARB containing product.
- Statins – caution is advised. See SPC for further information.
- PDE-5 Inhibitors (e.g. sildenafil) – risk of significant blood pressure reduction-caution is advised.
- Medicines that increase the amount of potassium in the blood. These include potassium supplements, salt substitutes containing potassium, potassium-sparing medicines and heparin. Monitoring of serum potassium is recommended if Entresto® is co-administered with these agents.
- NSAIDs or selective Cox-2 inhibitors - monitoring of renal function is recommended when initiating or modifying treatment in patients on Entresto® who are taking NSAIDs concomitantly
• Lithium - Do not take with Sacubitril/Valsartan (Entresto®)
• Co-administration with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampicin, ciclosporin), OAT1 (e.g. tenofovir, cidofovir) or MRP2 (e.g. ritonavir) may increase the systemic exposure of sacubitril or valsartan. Appropriate care should be exercised when initiating or ending treatment with such drugs
• Metformin - Co-administration with metformin reduced both Cmax and AUC of metformin by 23%. The clinical relevance of these findings is unknown. When initiating therapy with Entresto® in patients receiving metformin, the clinical status of the patient should be evaluated.

Monitoring
Monitoring of Sacubitril/Valsartan is the same as for ACE inhibitors or angiotensin receptor blockers.

Blood pressure should be monitored regularly (6 weeks, 3 months, 6 months and then every 6 months thereafter). If symptomatic hypotension occurs during treatment with Sacubitril/Valsartan, it is advisable to decrease the prescribed dose or discontinue Sacubitril/Valsartan. Specialist advice or referral may be required. See SPC for further information.

Renal function must be checked regularly (6 weeks, 3 months, 6 months and then every 6 months thereafter). Serum potassium may require more frequent monitoring, especially in patients who have risk factors, such as diabetes mellitus or hypoaldosteronism, any patient who is on a high potassium diet or on mineralocorticoid antagonists (i.e. spironolactone or eplerenone). If patients experience clinically significant hyperkalaemia, adjustment of concomitant medicinal products, or temporary down-titration or discontinuation is recommended. If serum potassium level is >5.4 mmol/L, advice from a heart failure specialist should be sought and discontinuation should be considered.

Annual FBC and liver function tests should be performed.

Patients who are taking Sacubitril/Valsartan may develop worsening heart failure. It may become appropriate to refer patients back to secondary care or local heart failure clinic for assessment if any of the following are present:

• Worsening heart failure symptoms
• Recent heart failure hospital admissions
• Shocks from implantable cardioverter-defibrillator (if present)
• Increasing diuretic requirement
• Decreasing tolerance of heart failure medical therapy (ACE-inhibitor, ARB, ARNI, beta-blocker or Mineralocorticoid Antagonist). See also discussion regarding blood pressure and serum potassium under monitoring.
• Worsening renal function

It is important to exercise clinical judgement. Referral to supportive/palliative care may be more appropriate if it has previously been agreed that this would appropriate in the event of deterioration. For elderly patients, referral to a Care of the Elderly Specialist may be more appropriate.

References