North Central London
Joint Formulary Committee

Factsheet

Sacubitril valsartan (Entresto®) ▼

for chronic heart failure with reduced ejection fraction

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FACTSHEET TO FACILITATE PRESCRIBING

PLEASE NOTE THIS IS NOT A SHARED CARE GUIDELINE, NOR IS IT A FULL SUMMARY OF DRUG INFORMATION. ALWAYS REFER TO THE MOST RECENT BNF AND/OR SUMMARY OF PRODUCT CHARACTERISTICS.

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NCL JFC is funded by and provides advice to Acute Trusts and Clinical Commissioning Groups in NCL.

Factsheet – Sacubitril valsartan (Entresto®)▼

Chronic heart failure with reduced ejection fraction

As per local formulary agreement

SECONDARY CARE

- Sacubitril valsartan should be ***initiated in specialist secondary care***, under the direction of consultant with an established expertise in managing patients with heart failure and access to a multidisciplinary team.
- ***Dose titration*** should be performed in secondary care.

PRIMARY CARE

- ***Transfer to primary care*** should occur once patients are fully optimised on the maximal tolerated dose of sacubitril valsartan.
- ***Monitoring*** should be performed in primary care, as detailed below.

Checklist and actions for GP:

- **Ensure that the patient's repeat prescription for ACE inhibitors or ARBs is stopped**
- Ensure documented communication has been received from a consultant specialising in heart failure with an indication for use and evidence that the specialist has counselled the patient on sacubitril valsartan (benefits, side effects/risks)
- Ensure that the patient meets criteria for continuation of treatment (i.e. symptomatic heart failure [NYHA II to IV] with reduced ejection fraction [left ventricular ejection fraction ≤35%] despite optimal treatment with ACEi/ARB, β blocker and spironolactone/ eplerenone)
- Conduct necessary blood test monitoring at agreed schedule (see Clinical Monitoring section)
- Prescribe routine supplies of sacubitril valsartan
- Monitor the patient's overall physical health and well-being.
- Consider stopping the drug and refer patient back to the consultant if the patient:
  - Is intolerant of side effects
  - Is non-compliant with medicines (or this is suspected)
  - Has a change in circumstances affecting sacubitril valsartan (e.g. pregnancy, deterioration of renal function)
- Ensure monitoring is carried out according to NICE clinical guidelines (CG108).

Dose and Administration

Sacubitril valsartan should be taken orally twice-daily. Sacubitril valsartan can be taken with or without food.

- Usual starting dose: 49 mg/51 mg twice-daily
- Usual maintenance dose: 97 mg/103 mg twice-daily

Renal impairment:

When initiating treatment:

- eGFR >60 mL/min/1.73m^2: no dose adjustment
- eGFR 30-60 mL/min/1.73m^2: starting dose of 24 mg/26 mg twice-daily
- eGFR 15-30 mL/min/1.73m^2: limited experience, not recommended
- eGFR <15 mL/min/1.73m^2: no experience, not recommended

Patients with mild and moderate renal impairment are more at risk of developing hypotension. If a patient's renal function deteriorates significantly with no obvious precipitants (e.g. dehydration or intercurrent illness) or the patient develops hyperkalaemia, adopt the same management as would be taken for an ACEi (e.g. stop sacubitril valsartan, repeat blood tests and if necessary prior to restarting sacubitril valsartan, discuss the case with the initiating consultant).

Hepatic impairment:

- Child-Pugh A: No dose adjustment is required
- Child-Pugh B or AST/ALT x2 upper normal limit: starting dose of 24 mg/26 mg twice-daily
- Child-Pugh C: contraindicated

Discontinuing treatment: if sacubitril valsartan is discontinued, the patient should be restarted on their previous ACEi/ARB after 36 hours. The ACEi/ARB should be titrated back to the maximum tolerated dose.

Adverse Effects

Very common (≥10%): Hypotension (systolic blood pressure [SBP] ≤95 mmHg, symptomatic hypotension), hyperkalaemia, renal impairment.

- In the clinical trial setting, hypotension occurred with greater frequency with sacubitril valsartan compared to ACEi, however hyperkalaemia and renal impairment occurred at a lower frequency.
  - Hypotension: Temporary down-titration or discontinuation of sacubitril valsartan is recommended. Dose adjustment of diuretics, concomitant antihypertensives and treatment of other causes of hypotension (e.g. hypovolaemia) should be considered.
  - Hyperkalaemia: Adjustment of concomitant medicinal products (e.g. spironolactone/ eplerenone, or other drugs) temporary down–titration or discontinuation is recommended. If serum potassium level is >5.4 mmol/l discontinuation should be considered.
  - Renal impairment: Correction of dehydration (including reduction or decrease in diuretics) or cessation of concomitant use of non-steroidal anti-inflammatory agents. Down-titration should be considered in patients who develop a clinically significant decrease in renal function.

Serious: Angioedema

- 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.

- Black patients have an increased susceptibility to develop angioedema
- In the clinical trial setting, angioedema occurred with greater frequency with sacubitril valsartan compared to ACEi

Sacubitril valsartan is a black triangle drug and as such is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions using the Yellow Card Scheme.

Contraindications

- Concomitant use with ACE inhibitors due to the increased risk of angioedema. Sacubitril valsartan must not be administered until 36 hours after discontinuing ACE inhibitor therapy.
  - Primary care prescriber must ensure the ACE inhibitor is removed completely from the patient's repeat prescription.
- Concomitant use with aliskiren-containing medicinal products
- Known history of angioedema related to previous ACE inhibitor or ARB therapy.
- Hereditary or idiopathic angioedema
- Severe hepatic impairment (Child-Pugh C), biliary cirrhosis and cholestasis
- Second and third trimester of pregnancy (additionally not recommended during the first trimester of pregnancy)
- Hypersensitivity to the active substances or to any of the excipients

Special Warnings and Precautions for Use

- Concomitant use with ACE inhibitor, ARB or aliskiren (also see 'Contraindications')
  - Sacubitril valsartan must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy
  - Primary care prescriber must ensure the ACE inhibitor is removed completely from the patient's repeat prescription.
  - Patient and carers must be counselled to return ACE inhibitors to pharmacy for safe destruction and advised to not take ACE inhibitor.
- Treatment should only be initiated if SBP is ≥100 mmHg (cases of symptomatic hypotension have been reported, especially in patients ≥65 years old, patients with renal disease and patients with low SBP [<112 mmHg]. See 'Adverse effects')
- Impaired renal function (see 'Dosing and administration' and 'Adverse effects')
- Hyperkalaemia (see 'Adverse effects')
- Angioedema (see 'Adverse effects')
- Patients with renal artery stenosis
- Hepatic impairment (see 'Dosing and administration')

Pregnancy and Breastfeeding: The use of sacubitril valsartan is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy. Sacubitril valsartan is not recommended during breast-feeding.

Drug Interactions

- ACE inhibitors – see 'Contraindications'
- ARB – sacubitril valsartan contains valsartan, and therefore should not be co-administered with another ARB containing product

- Aliskiren – see 'Contraindications'. Combination of sacubitril valsartan with aliskiren is potentially associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure)
- Statins – there is a potential that sacubitril valsartan may increase exposure with concomitant statins (in vitro data), however, dose reduction should be undertaken on a case by case basis i.e. consider reducing dose of statin if on maximum dosage, if deemed high risk of side effects from statins or if patients exhibit side effects after initiation.
- PDE5 inhibitors including sildenafil (Viagra®), tadalafil (Cialis®) – increased risk of hypotension, warn the patient of the risk of hypotensive symptoms e.g. light-headedness, dizziness
- Drug that may increase potassium or creatinine. Monitor renal function and electrolytes if any of the following are started or titrated upwards
  - Amiloride or triamterene
  - Spironolactone or eplerenone
  - Non-steroidal anti-inflammatory drugs (NSAIDS)
  - Heparin including dalteparin, tinzaparin and enoxaparin
  - Ciclosporin, tacrolimus, pentamidine, co-trimoxazole, ketoconazole, metyrapone
- Lithium – increase in lithium concentrations, monitor lithium levels carefully
- Metformin – co-administration with sacubitril valsartan may lead to lower levels of metformin (AUC reduced by 23%). The impact of this interaction in clinical practice is unknown so changes to metformin therapy should be based on patient response and may require dose increase or an alternative agent to control diabetes.
- OATP and MRP2 transporters – Drugs such as rifampicin, ciclosporin, tenofivir, cidofivir or ritonavir may increase systemic exposure to sacubitril valsartan and as such lower doses of sacubitril valsartan should be initiated then dose adjusted according to response. Similarly if these medicines are ceased, according to patient response, the dose of sacubitril valsartan may need to be increased

Please refer to SPC/BNF for full information on interactions with drug name and how to manage these interactions.

Clinical Monitoring

All patients with chronic heart failure require monitoring in line with NICE CG108. This monitoring should include:

- a clinical assessment of functional capacity, fluid status, cardiac rhythm (minimum of examining the pulse), cognitive status and nutritional status
- a review of medication, including need for changes and possible side effects
- serum urea, electrolytes, creatinine and eGFR

More detailed monitoring will be required 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 required at least 6-monthly for stable patients with proven heart failure.

At the time of approval no specific monitoring, over-and-above usual monitoring requirements for patients with heart failure, was required for sacubitril valsartan. Primary care clinicians should review

their patients as per their normal practice. However, sacubitril valsartan is a black triangle drug and any suspected adverse reactions should be reported using the Yellow Card Scheme.

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References

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2) NICE Clinical Guideline 108 'Chronic heart failure in adults: management'. Available at https://www.nice.org.uk/guidance/CG108/chapter/1-Guidance#monitoring
3) NICE TA388 'Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction'. Available at https://www.nice.org.uk/guidance/ta388