NHS

County Durham & Tees Valley
Area Prescribing Committee

Prescribing guidance – Sacubitril Valsartan

Drug	Sacubitril Valsartan (Entresto®)
Specialty	Cardiology
Background	Sacubitril Valsartan is indicated for the treatment symptomatic heart failure in adult patients with a reduced ejection fraction. It should be used instead of ACE inhibitor or Angiotensin Receptor Blocker (ARB). It improves mortality and reduces hospital admissions.
Patient criteria	Patients initiated on Sacubitril Valsartan should fulfil the following criteria: ▪ Patients with PERSISTANT severe left ventricular impairment (Ejection fraction <35%) ▪ Symptomatic (NYHA II to IV) despite optimal treatment with beta blocker, ACE inhibitor or ARB and eplerenone or spironolactone (MRA) for at least 3 months ▪ Recent (within the last 4 weeks) serum potassium ≤ 5.4mmol/L ▪ Recent (within the last 4 weeks) eGFR ≥ 30ml/min/1.73m^2 ▪ Systolic blood pressure >100mmHg ▪ Seen and identified by consultant cardiologist ▪ Access to a specialist heart failure nurse, to manage and monitor patient during the initiation and stabilisation of treatment
Contra-indications to use	**Sacubitril Valsartan must not be co-administered with ACE inhibitor, Angiotensin Receptor Blocker (ARB)(INCREASED RISK OF ANGIOEDEMA) or Aliskiren.** Systolic blood pressure < 100mmHg eGFR < 30ml/min/1.73m^2 Serum potassium > 5.4mmol/L
Before initiation	**Allow a 36 hour washout of the patient's ACE inhibitor, ARB or Aliskiren.** Ensure baseline renal function and potassium have been measured and within acceptable limits and systolic blood pressure > 100mmHg.
Initiation, titration and monitoring	The recommended starting dose is Sacubitril Valsartan 49mg/51mg twice daily. Sacubitril Valsartan should be prescribed using the generic name to avoid concomitant prescribing of ACE-I or additional ARB therapy. If repeat renal function and serum potassium levels on initial treatment are within acceptable limits and systolic blood pressure is > 100mmHg, the dose should be doubled at two weekly intervals to a target dose of 97mg/103mg twice daily, as tolerated. *A lower starting dose of Sacubitril Valsartan 24mg/26mg twice daily is recommended if:* *Systolic Blood Pressure between 100 and 110mmHg eGFR 30 to 60ml/min/1.73m^2* *Patient is ACE inhibitor or ARB naïve* *Patient only tolerated lower doses of ACE inhibitor or ARB* *AST/ALT > 2 x ULN* *Patients starting on this lower dose should be titrated at a lower rate. Allow 3 to 4 weeks between dose titrations.* Continue to review and monitor the patient, including checking blood pressure and renal function and electrolytes, until clinically and biochemically stable. Once maximum tolerated dose is achieved please inform the GP with clear instruction of the dose to enable continued prescribing and ongoing management from the GP. Patients will be reviewed every six months in primary care, with repeat measurement of renal function, electrolytes and blood pressure (three monthly if on concomitant eplerenone or spironolactone) or more frequently if there are concerns regarding change in renal function and/or electrolytes. The most common adverse effects are hypotension, hyperkalaemia and renal impairment. See overleaf for management of these.

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Patient Education

Ensure that the patient has appropriate information and education about Sacubitril Valsartan.

Ensure that they understand not to take an ACE inhibitor, ARB or Aliskiren if they are taking Sacubitril Valsartan. Advise that all ACE inhibitors and ARBs are removed from patient's home to avoid inadvertent co-administration.

Provide the patient and/or carer with an "Entresto alert card"

Ensure that the patient has a telephone contact number for the Heart Failure Specialist Team.

Clinically important interactions

(see BNF or SPC for full details)

Interacting drug	Comment/ Action
ACE inhibitor	**Avoid co-administration. Dual blockade of the renin-angiotensin system significantly increases the risk of angioedema**
ARB	Avoid prescribing additional ARB as Entresto contains Valsartan
Aliskiren	Increases risk of renal impairment. Contraindicated in patients with diabetes mellitus or with eGFR<60ml/min.
NSAIDs	Increased risk of renal dysfunction – avoid
Statins	May cause increased levels of statin – consider halving the dose of the statin
PDE5 inhibitors Eg sildenafil, tadalafil, vardenafil	Use with caution as may cause significant reduction in blood pressure.
Lithium	This combination has not been investigated but reversible increases in lithium levels reported with ACE inhibitors and ARBs. If combination is necessary monitor lithium levels closely.

Adverse events

Adverse Event	Incidence	Comment
Angioedema	0.5%	Discontinue sacubitril valsartan if occurs. 2.4% if of black origin
Symptomatic hypotension	18%	Review other medication and consider adjusting those that may contribute to hypotension. Consider reducing sacubitril valsartan dose or stopping
Hyperkalaemia	16%	Dose reduction should be considered if level is 5.0mmol/L or greater. If potassium level is > 5.4mmol/L, discontinue and seek further advice from HF team.
Worsening renal dysfunction	10%	An increase in creatinine of up to 50% above baseline or an increase in potassium to ≤5.4 mmol/L are acceptable but consider reducing the dose. If potassium rises to >5.4 mmol/L or creatinine increases by >100%, discontinue and seek further advice from HF team

Other information

Tablets available:

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

The manufacturer's SPC states that "Entresto" should be stored in the original packaging in order to protect it from moisture. The manufacturer cannot provide any further information regarding storage in compliance aids, therefore, at the present time, this cannot be recommended.

Further reading

NICE Technology Appraisal Guidance (TA388). Sacubitril/valsartan for treating symptomatic chronic heart failure with reduced ejection fraction. April 2016

McMurray JJ et al. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure (PARADIGM HF). NEJM 2014, 37; 11: 993-1004

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