

Sacubitril valsartan (Entresto®)

For the treatment of symptomatic chronic heart failure with reduced ejection fraction Advice for Prescribers

1. Introduction:

Sacubitril valsartan (Entresto®) is licensed for the treatment of symptomatic chronic heart failure with reduced ejection fraction. Sacubitril valsartan is an angiotensin receptor neprilysin inhibitor, including both a neprilysin inhibitor (sacubitril) and an angiotensin II receptor blocker (ARB; valsartan). Both sacubitril and valsartan lower blood pressure. The PARADIGM-HF study compared sacubitril/valsartan to enalapril and demonstrated superiority with respect to reduction in the risk of cardiovascular death and reduction in the number of first hospital admission relating to heart failure (overall 20% relative risk reduction). Sacubitril/valsartan also had a lower rate of all-cause mortality (16% relative risk reduction). It is approved by NICE (NICE TA 388).

It is an oral tablet, available as:

Sacubitril 24mg / valsartan 26mg

Sacubitril 49mg / valsartan 51mg

Sacubitril 97mg / valsartan 103mg

Sacubitril valsartan is an amber specialist initiation drug; it should only be initiated by a heart failure specialist – either a Heart Failure Specialist Nurse (HFSN) or a Cardiologist. In NHS Vale of York the Cardiologist or Heart Failure Specialist Nurse (HFSN) will initiate, the HFSN will monitor and titrate and then transfer to GP when on an optimised dose. The exception is in Pocklington (as there is no HFSN provision) the titration and monitoring will be done by the hospital HFSN in clinic. The patient will be provided with 30 days prescription on initiation in case there are delays in getting a GP prescription or time for the community pharmacist to order in.

2. Background to initiation by specialist:

Inclusion criteria

Adult patients that meet the following criteria:

- Diagnosis of heart failure with proven left ventricular systolic dysfunction ($EF \leq 35\%$) **AND**
- NYHA II-IV symptoms **AND**
- Already dose titrated and stable on ACE inhibitor or ARB (for ≥ 2 weeks)

Exclusion criteria

- Children under 18 years
- Hypersensitivity to sacubitril/valsartan or component parts
- Concomitant use with ACE inhibitors, ARBs or aliskiren
- History of angioedema including with ACE inhibition or ARB
- Pregnancy and Breast feeding
- Systolic BP (SBP) < 100 mmHg
- $eGFR < 30$ ml/min/1.73m²
- $K > 5.4$ mmol/L
- Moderate/severe aortic stenosis or outflow tract obstruction
- Known renal artery stenosis
- Hereditary or idiopathic angioedema
- Severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh class C)
- Patients who refuse treatment under a protocol

3. Drug information

Interactions include:

- Potassium sparing diuretics or aldosterone antagonists- Monitor potassium
- Lithium –monitor lithium levels if co-administration is required.
- Avoid NSAIDs whilst on sacubitril/valsartan®
- Statins – use with caution. In vitro data showed that sacubitril valsartan *may* increase the level of statin in the blood and hence *may* increase adverse effects related to statin. Any concerns should be raised with a specialist.
- see BNF for further information on interactions

Contraindications to sacubitril/valsartan

- Concomitant use with ACE inhibitor, ARB or aliskiren
- Known history of idiopathic angioedema or angioedema related to previous ACE inhibitor or ARB therapy
- Systolic blood pressure <100mmHg
- Renal disease with eGFR <30 ml/min/1.73m² or severe hepatic impairment

Cautions

- Increased risk of hypotension in:
- Patients >65 years old
- Patients with renal impairment (eGFR <60ml/min/1.73m²)
- Patients hypotensive systolic blood pressure<110mmHg

Adverse effects

Most common reported side effect is hypotension. As for other ARBs, sacubitril valsartan can cause hyperkalaemia and renal dysfunction.

U&Es and blood pressure will be monitored by community heart failure nurses or while inpatient.

Dose

Usual starting dose is one 49mg/51mg tablet twice a day reviewed after 2-4 weeks and, if tolerated, increased to the maximal target dose of one 97mg/103mg tablet twice a day.

Lower starting dose of 24mg/26mg may be used for patients with low blood pressure, eGFR 30-60 ml/min/1.73m² or patients not already established on full dose ACE inhibitor (e.g. ramipril 10mg daily). For these patients dose titration may be done every 3-4 weeks.

4. Key points for GPs:

- Has the drug been started by a heart failure specialist with access to a multidisciplinary heart failure team?
If not, do not prescribe but refer to heart failure specialist - GPs should not initiate.
- The patient should have been provided with an alert card by the heart failure specialist
- Is the patient on a stable dose?
Heart failure specialist should monitor AND titrate dose. Only when patient is on a stable dose should they be transferred to GP prescribing.
- The patient's GP should be informed in writing:
 - About initiation of the drug
 - Any special considerations they need to be aware of for that patient
- Has the patient been booked for a follow-up appointment with a member of the multidisciplinary heart failure team?
- GP to complete medicines reconciliation on GP Clinical system to ensure that previous ACEI or ARB are removed from medication list (**ACE Inhibitors, ARBs and Aliskiren must not be given concomitantly with sacubitril valsartan**)
- Monitoring – see point 5

IMPORTANT for ACE inhibitors ONLY: a minimum 36 hour 'wash out period' is required when changing patients from an ACE inhibitor to sacubitril/valsartan or if changing back from sacubitril/valsartan to an ACE inhibitor.

5. GP monitoring

The GP is required to undertake 6 monthly U&Es and BP check.

6. Practical advice

- Swallow whole with glass of water. Tablets can be taken with or without food
- Follow sick day rules for ACE/ARB
- Increased risk of hypotension in patients >65 years or with eGFR < 60 ml/min/1.73m²
- Avoid NSAIDs
- Beware of low salt substitutes which can have high potassium content