Oxford University Hospitals NHS
NHS Trust

NHS
Oxfordshire
Clinical Commissioning Group

Shared Care Protocol: Use of sacubitril valsartan for the treatment of symptomatic chronic heart failure with reduced ejection fraction.

This protocol provides prescribing and monitoring guidance for sacubitril valsartan therapy. It should be read in conjunction with the Summary of Product Characteristics (SPC) available on www.medicines.org.uk/emc and the BNF.

Shared Care Responsibilities

Shared care assumes communication and agreement between the specialist, GP and patient. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy.

Specialist: Cardiologists/ Heart failure team

- To discuss sacubitril valsartan treatment with the patient and ensure the decision to start treatment is agreed between the patient and the prescriber. The patient will be provided with a patient information leaflet about the therapy and specific information about stopping ACEi / ARB therapy, the complications of therapy and their role in reporting adverse drug reactions promptly to either the Heart Failure (HF) team or the GP. The specialist should be satisfied that the patient understands the information supplied and the importance of adhering to treatment.
- Initiate and monitor sacubitril valsartan treatment in line with local and NICE guidance and continue to prescribe until the patient is stabilised on therapy. To contact GP by letter or email once the decision to initiate sacubitril valsartan therapy has been made to formally request agreement with the GP to shared care. If sacubitril valsartan is initiated as an in-patient the patient will be discharged with a supply and a plan made within the HF team for review and supply of sacubitril valsartan until the dose is optimized.
- To communicate to the GP if the patient will attend the surgery for monitoring blood tests during the up-titration phase (for logistical reasons only – results will be followed up by specialist team).
- To liaise with the GP regarding changes in disease management, drug dose and missed clinic appointments.
- Be available to give advice to GP and patient at any time throughout treatment (contact as below).

GP

- Prescribe long term sacubitril valsartan once the dose is stable and shared care is agreed.
- To ensure long term prescribing of sacubitril valsartan is in line with local and NICE guidance, once patient has been stabilised on treatment by cardiologist /HF team.
- Contact heart failure team at any time during therapy for further advice regarding shared care.
- To be aware that a patient may come to the surgery for blood tests during initial up-titration phase if patient cannot make frequent journeys to OUH. The GP is not responsible for reviewing any of these results during the initiation and up-titration phase.
- To monitor BP renal function, serum potassium at least 6 monthly during therapy, as for an ACE inhibitor or ARB.

Patient

- Agree to read through the information supplied about therapy and discuss with heart failure team to ensure information is understood.
- Agree to treatment and monitoring only after making an informed decision.
- Agree to being under the shared care of the GP and specialist.
- Agree to attend for blood tests and monitoring when required.
- Report any side effects to the GP or a member of the specialist team.

Written by Joanne Coleman, Helen Jackson and Dr James Gamble April 2020 (Based on Prescribing guidance produced by South East London Area Prescribing Committee) Approved by APCO March 2020. Review March 2022

Background for Use

Sacubitril valsartan▼ (Entresto®) is a dual acting angiotensin blocker and neprilysin inhibitor (ARNI), inhibiting the renin angiotensin aldosterone system and the breakdown of vasoactive peptides. It is licensed and approved by the National Institute for Health and Care Excellence (NICE; TA 388 April 2016) and is recommended as an option for the treatment of symptomatic chronic heart failure (HF) with reduced ejection fraction[1,2]. The pivotal clinical evidence is provided by the PARADIGM-HF trial[3], which showed that sacubitril valsartan was more clinically effective than enalapril at reducing overall mortality and reducing hospitalizations. Subsequent studies have confirmed highly beneficial effects on inpatients with acute heart failure, and that cardiac function improves in 75% of patients treated with the drug[4,5].

In Oxfordshire, sacubitril valsartan may be considered for initiation by the specialist cardiology / heart failure team for treating chronic HF in patients meeting all of the following criteria:

1. New York Heart Association (NYHA) class II to IV symptoms
2. Left ventricular ejection fraction of 40% or less
3. Taking a stable dose of angiotensin-converting enzyme inhibitors (ACEi) or an ARB

The HF team will provide initial patient screening for suitability of therapy and counselling, initiation and up-titration of dose, monitoring during up-titration phase and ensure the patient is stabilised on sacubitril valsartan (maximum tolerated dose for at least one month, in line with NICE recommendations).

ACEi or ARB therapy MUST BE DISCONTINUED at least 36 hours before starting sacubitril valsartan.
Prescribe sacubitril valsartan using generic name to avoid concomitant use of ACEi or ARB therapy

Contraindications and Precautions

Contraindications (for details see BNF or SPC)	Cautions (for details see BNF or SPC)
• Hypersensitivity to the active substance / excipients • **Concomitant use with ACEi.** Sacubitril valsartan must not be administered until 36 hours after discontinuing ACEi therapy. • **Concomitant use with another ARB** (as the combination drug contains valsartan) • Concomitant use with aliskiren containing products in patients with diabetes mellitus. Also avoid concomitant use with aliskiren containing products in patients with renal impairment (eGFR less than 60ml/min/1,73m^2) • Known history of angioedema related to previous ACEi or ARB therapy • Hereditary or idiopathic angioedema • Systolic blood pressure (SBP) less than 100mmHg • End stage renal disease • Bilateral renal artery stenosis • Serum potassium greater than 5.4mmol/L • Severe hepatic impairment, biliary cirrhosis and cholestasis (Child-Pugh C) • Pregnancy and breast feeding • For contra-indications for use with other medicines see Notable Drug Interactions	• Serum potassium levels greater than 5mmol/L • Renal artery stenosis • Renal impairment. Patients with eGFR less than 30ml/min/1.73m^2 are at greater risk of hypotension • Moderate hepatic impairment (Child-Pugh B) or with alanine transaminase (ALT) / aspartate aminotransferase (AST) values more than twice the upper limit of normal • Dehydration due to risk of worsening renal function • NYHA class IV – patients will not routinely be started on treatment • For cautions for use with other medicines see Notable Drug Interactions

BNF = British National Formulary; SPC = Summary of Product Characteristics

Dosage – Initiation and up-titration – done by specialist team

The starting dose is one tablet of **49mg/51mg TWICE daily**, to be taken with water, with or without food. The dose should be doubled at 2 to 4 weeks to the target dose of one tablet of 97mg/103mg TWICE daily.

A reduced starting dose of one tablet of 24mg/26mg TWICE daily with a slow dose titration (doubling every 3 to 4 weeks) should be considered for patients with:

- Systolic blood pressure between 100 to 110mmHg
- Moderate renal impairment (eGFR 30 to 60ml/min/1.73m^2). Note for patients with severe renal impairment (eGFR less than 30ml/min/1.73m^2), sacubitril valsartan should be used with caution due to very limited experience and greater risk of hypotension.
- Moderate liver impairment (Child-Pugh B classification or with AST/ALT greater than twice the upper limit of normal range) – use with caution due to limited clinical experience.

Note: The valsartan within sacubitril valsartan is more bioavailable then that in other formulations; 26mg, 51mg and 103mg of valsartan in sacubitril valsartan is equivalent to 40mg, 80mg and 160mg in other formulations, respectively.

Time to Response

The beneficial effect of sacubitril valsartan has been shown in studies to start within days to weeks.

Pre-Treatment Assessment and monitoring during up-titration phase by HF team

Prior to initiation and before and after each dose titration the following should be monitored:

- Blood pressure
- Renal function
- Electrolytes including serum potassium
- Liver function and full blood count (initiation only)

Note: For logistical reasons it may be necessary for the patient to visit the GP in order to have blood taken for the monitoring during the up-titration phase. The HF team should provide a blood card from OUH for these tests and will be responsible for reviewing the results.

Ongoing monitoring by GPs

NICE CG (106) Chronic Heart Failure recommends at least 6 monthly reviews of patients which should include monitoring BP, renal function, serum potassium during therapy, as for an ACE inhibitor or ARB.

Actions to be taken / Back-up information and advice

The HF team may be contacted for advice regarding tolerability, side effects or potential complications of sacubitril valsartan therapy any time during treatment. Patients may also be referred back to the HF team if necessary. See below for contact details (page 6).

Side Effects	Actions to be taken
Hypotension	Review medication and consider adjusting any other medicines that are contributing to low blood pressure or review the dose of sacubitril valsartan which may need to be reduced. Consider discontinuing therapy if SBP is consistently below 100mmHg despite above measures, particularly if symptomatic hypotension. We suggest discussion with heart failure team, as many heart failure patients may tolerate hypotension without symptoms
Hyperkalaemia	Consider dose reduction where the potassium level is 5.5mmol/L or greater. Discontinue sacubitril valsartan if potassium level is 6.0mmol/L or greater and contact HF team for advice. See advice below for AKI.
Renal Impairment	Monitor renal function closely if eGFR trending downwards. In severe renal impairment (eGFR less than 30ml/min/1.73m2) contact HF team for advice.
Acute renal impairment / acute kidney injury / rise in creatinine	Treat in the same way as patients taking ACEi or ARB, and as per OCCG guidelines[7]. If AKI 2-3, review the patient for clinical assessment within the suggested timeline. Hold sacubitril valsartan until renal function returns to baseline, then re-introduce at half of the previously tolerated dose, or 24mg/26mg twice daily if previously taking lowest dose and check renal function and electrolytes 1 week later. If vital signs and renal function allow, double the dose back to the original dose after four weeks and check renal function and electrolytes 1 week later. Please see the recent guidance from the heart failure and renal societies for more detail on dealing with renal issues in heart failure patients.[8] This guidance is also summarised here: http://heartfailureoxford.org.uk/gp/renal/
Hepatic impairment	Severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification) discontinue sacubitril valsartan. Moderate liver impairment; consider dose reduction (Child-Pugh B classification).
Angioedema	Discontinue sacubitril valsartan if angioedema occurs. Patient should be given appropriate therapy and monitored for airway compromise.

Other side effects include: anaemia, hypokalaemia, cough, nausea, diarrhoea and gastritis

Sacubitril valsartan is a black triangle drug – any adverse effect must be reported to the MHRA using the yellow card system and via the local incident reporting system.

Notable Drug Interactions (Refer to BNF and SPC for full details)

Drug / Drug class	Recommendation – for full details see BNF and SPC
ACEi	Avoid concurrent use and allow a washout period of at least 36 hours when switching between ACEi and sacubitril valsartan due to risk of angioedema
ARB	Avoid prescribing any additional ARBs as sacubitril already contains the ARB valsartan.
Aliskiren	Avoid concurrent use due to increased frequency of adverse effects such as hypotension, hyperkalaemia and renal impairment
Loop Diuretics	Clinical experience thus far is that sacubitril valsartan frequently potentiates the effects of loop diuretics, and doses may need to be reduced in some patients.
Potassium sparing diuretics, mineralocorticoid antagonists, potassium supplements, salt substitutes or any agent that increases potassium	Monitoring of serum potassium is recommended due to risk of hyperkalaemia
Statins	Sacubitril valsartan increased the plasma concentration of atorvastatin and its metabolites. Caution should be exercised when co-administering statins
Phosphodiesterase type 5 (PDE5) inhibitors e.g. sildenafil, tadalafil, vardenafil	Concomitant use can result in a significant reduction in blood pressure after a single dose. Caution should be exercised if a PDE5 inhibitor is initiated
Nitrates	Co-administration may reduce heart rate, in general no dosage adjustment is required
Non-steroidal anti-inflammatory drugs (NSAIDs) including cyclo-oxygenase-2 (COX-2) inhibitors	Concomitant use of sacubitril valsartan and an NSAID can worsen renal function – generally avoid combination. If concomitant use is necessary close monitoring of renal function is required.
Lithium	ACEi and ARBs are known to cause reversible increases in lithium levels and toxicity, therefore the concomitant use of sacubitril and valsartan is not recommended, if unavoidable close monitoring of lithium levels is necessary
Metformin	Sacubitril valsartan can reduce the plasma concentration of metformin, monitor blood sugars and adjust metformin dose if necessary
Metabolic interactions	Caution should be exercised with the co-administration of sacubitril valsartan with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampicin, ciclosporin), OAT1 (tenofovir, cidofovir) or MRP2 (e.g. ritonavir) as these may increase levels of the sacubitril active metabolite or of valsartan

Contact details

Contact the heart failure team if any queries/ concerns: telephone 01865 223067, email heartfailure.nurse@nhs.net,
or Community Heart Failure Nurses 01865 904808, email oxfordhealth.communityheartfailure@nhs.net

References

1. NICE TA 388 Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction. April 2016. www.nice.org.uk/guidance/ta388
2. SPC Entresto. Novartis 5th Feb 2016 www.medicines.org.uk/emc/medicine/31244
3. PARADIGM-HF study. N Engl J Med 2014; 371: 993-1004
4. Velazquez, NEJM 380,: 539–48. https://doi.org/10.1056/NEJMoa1812851.
5. Januzzi, et al. 'Association of Change in N-Terminal Pro–B-Type Natriuretic Peptide Following Initiation of Sacubitril-Valsartan Treatment With Cardiac Structure and Function in Patients With Heart Failure With Reduced Ejection Fraction'. JAMA 322, 2019: 1085–95.
6. NICE Guidelines on Chronic Heart failure (NG106) September 2018. www.nice.org.uk/guidance/ng106
7. OCCG renal guidance: https://clinox.info/clinical-support/local-pathways-and-guidelines/?custom_in_SupportArea=51979
8. Clark AL et al Change in renal function associated with drug treatment in heart failure: national guidance. Heart 2019;105:904-910. https://heart.bmj.com/content/105/12/904.full