Barnsley Hospital NHS
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Clinical Commissioning Group

Shared Care Guideline for Entresto® in the management of Chronic Heart Failure

Introduction

Indication/Licensing information

Sacubitril valsartan (Entresto®) is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.

NICE recommends Sacubitril valsartan (Entresto®) as an option for treating symptomatic chronic heart failure with reduced ejection fraction, only in people:

- with New York Heart Association (NYHA) class II to IV symptoms and
- with a left ventricular ejection fraction of 35% or less and
- who are already taking a stable dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor-blockers (ARBs).

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 guideline NG106 Chronic heart failure in adults: diagnosis and management.

Pharmacology

Sacubitril: Neprilysin inhibitor; neprilysin is responsible for degradation of atrial and brain natriuretic peptide; the cardiovascular and renal effects of sacubitril's active metabolite (LBQ657) in heart failure are attributed to the increased levels of peptides that are degraded by neprilysin (eg, natriuretic peptide); administration results in increased natriuresis, increased urine cGMP, and decreased plasma MR-proANP and NT-proBNP.

Valsartan: Angiotensin II receptor type I inhibitor; decreases blood pressure and blocks vasoconstrictor and aldosterone-secreting effects of angiotensin II

Dosage and administration

Sacubitril valsartan is administered orally. The recommended starting dose is one 49/51 mg tablet, twice daily. The dose should be doubled at 2 to 4 weeks to the target dose of one 97/103 mg tablet (97.2 mg sacubitril and 102.8 mg valsartan) twice daily, as tolerated by the patient.

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.
- Patient's who have previously been taking low dose* of ACEi/ARB.

* Enalapril 10mg (or less), Lisinopril 10mg (or less), Ramipril 5mg (or less), Valsartan 160mg (or

less), Losartan 50mg (or less) and Olmesartan 10mg (or less).

Treatment should not be initiated in patients with serum potassium level >5.4 mmol/l or with SBP ≥100 to 110 mmHg.

Entresto 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, it must not be started for at least 36 hours after discontinuing ACE inhibitor therapy.

Renal impairment

- No dose adjustment is required in patients with mild (Estimated Glomerular Filtration Rate [eGFR] 60-90 ml/min/1.73 m^2) renal impairment.
- A starting dose of 24 mg/26 mg twice daily should be considered in patients with moderate renal impairment (eGFR 30-60 ml/min/1.73 m^2).
- As there is very limited clinical experience in patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) Entresto should be used with caution and a starting dose of 24 mg/26 mg twice daily is recommended.
- There is no experience in patients with end-stage renal disease and use of Entresto is not recommended.

Hepatic impairment

- No dose adjustment is required when administering Entresto to patients with mild hepatic impairment (Child-Pugh A classification).
- There is limited clinical experience in patients with moderate hepatic impairment (Child-Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. Entresto should be used with caution in these patients and the recommended starting dose is 24 mg/26 mg twice daily.
- Entresto is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification)

Available as: Sacubutril 24mg Valsartan 26mg film coated tablets
Sacubutril 49mg Valsartan 51mg film coated tablets
Sacubutril 97mg Valsartan 103mg film coated tablets

Responsibilities of the specialist initiating treatment

Summary

- To assess the suitability of the patient for treatment.
- To discuss the benefits and side effects of treatment with the patient/carer and the need for long term monitoring if applicable.
- To perform baseline tests and if appropriate routine tests until the patient is stable.
- To prescribe for the first 12 weeks of treatment
- To ask the GP whether they are willing to participate in shared care.
- To provide the GP with a summary of information relating to the individual patient to support the GP in undertaking shared care (See Shared care request form in Appendix A).
- To advise the GP of any dosage adjustments required, monitoring required, when to refer back, and when and how to stop treatment (if appropriate).
- To advise the GP when the patient will next be reviewed by the specialist.
- To monitor the patient for adverse events and report to the GP and where appropriate Commission on Human Medicines/MHRA (Yellow card scheme).
- To provide the GP with contact details in case of queries.

Baseline Tests

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)

Routine Tests:

Once the patient is stabilised on sacubitril valsartan therapy ongoing monitoring by the GP should include:

- Blood pressure, renal function and electrolyte monitoring every 6 months
- Liver function and full blood count monitoring every year

Disease Monitoring:

Once stable, review in clinic every 6 months.

Responsibilities of other prescribers

Acceptance of Responsibility by the Primary Care Clinician
It is optional for GPs to participate in taking on responsibility for shared care for the patient. GPs will take on shared care only if they are willing and able.

Summary
- To reply to the request for shared care as soon as possible.
- To prescribe and adjust the dose as recommended by the specialist.
- To ensure there are no interactions with any other medications initiated in primary care.
- To continue monitoring as agreed with secondary care (guideline should include details of monitoring requirements and what to do when each of the defined parameters alters).
- To refer back to the specialist where appropriate. For example:
  - Patient or general practitioner is **not** comfortable to continue with the existing regime due to either change in condition or drug side effects.
  - Advice in respect of concordance.
  - Special situations, (e.g. Pregnancy)
- Discontinue the drug as directed by the specialist if required
- To identify adverse events if the patient presents with any signs and liaise with the hospital specialist where necessary. To report adverse events to the specialist and where appropriate the Commission on Human Medicines/MHRA (Yellow card scheme).

Clinical Particulars

BNF therapeutic class	Sacubitril with Valsartan belongs to the Angeotensin II receptor antagonists, and Neprilysin inhibitors drug class
Contraindications	• 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
Cautions	• 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
Adverse Drug Reactions	Hypotension (Very common) - 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. Hyperkalaemia (Very common) - Consider dose reduction where the potassium level is 5mmol/L or greater. Discontinue sacubitril valsartan if potassium level is 5.4mmol/L or greater and contact Cardiology team for advice. Renal Impairment (Very common) - Monitor renal function closely if eGFR trending downwards. Consider dose reduction if moderate renal impairment (eGFR 30 to 60 ml/min/1.73m2). In severe renal impairment (eGFR less than 30ml/min/1.73m2) contact Cardiology team for advice. Angioedema (Uncommon) - Discontinue sacubitril valsartan if angioedema occurs. Patient should be given appropriate therapy and monitored for airway compromise.
Monitoring	• When initiating therapy or during dose titration with Entresto, blood pressure should be monitored routinely. If hypotension occurs, temporary down-titration or discontinuation of Entresto is recommended • Monitoring of serum potassium is recommended, especially in patients who have risk factors such as renal impairment, diabetes mellitus or hypoaldosteronism or who are on a high potassium diet or on mineralocorticoid antagonists • Monitoring of serum potassium is recommended if Entresto is co-administered with potassium-sparing diuretics (triamterene, amiloride), mineralocorticoid antagonists (e.g. spironolactone, eplerenone), potassium supplements, salt substitutes containing potassium or other agents. • Caution is required in patients with renal artery stenosis and monitoring of renal function is recommended. • monitoring of renal function is recommended when initiating or modifying treatment in patients on Entresto who are taking NSAIDs concomitantly
Interactions	**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. **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 increases 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. **NSAIDs** including cyclooxygenase-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.

Communication

Specialist to GP

The specialist will inform the GP when they have initiated sacubitril valsartan. When the patient is near completing the satisfactory initiation period, the specialist will write to the GP to request they take over prescribing and where possible give an indication as to the expected length of treatment. The Specialist will also send a Shared care request form to support the GP in undertaking shared care. (Appendix A)

GP to specialist

If the GP has concerns over the prescribing of sacubitril valsatran, they will contact the specialist as soon as possible.

Contact names and details

Contact Details	Telephone number	Email
Dr David Robson, Consultant Cardiologist	01226 432169	d.robson1@nhs.net
Dr Abdul Negahban, Consultant Cardiologist	01226 432572	a.negahban@nhs.net

Dr Deoraj Zamvar, Consultant Cardiologist	01226 432169	deoraj.zamvar@nhs.net
Dr Naeem Tahir, Consultant Cardiologist	01226 432169	naeem.tahir@nhs.net
Gillian Turrell, Lead Pharmacist - Medicines Information and Cardiology	01226 432857	gilliansmith2@nhs.net
Daniel Kaye, Cardiology Nurse Specialist	01226 434981	danielkaye@nhs.net
Nicola Wilkinson, Cardiology Nurse Specialist	01226 434981	n.wilkinson@nhs.net
Mark Balchin, Cardiology Nurse Specialist	01226 434981	markbalchin1@nhs.net

References

- British National Formulary. Available at: www.medicinescomplete.com/mc/bnf/current/
- Summary of Product Characteristics for Entresto. Available at: https://www.medicines.org.uk/emc/product/7751
- NICE TA388. Available at: https://www.nice.org.uk/guidance/ta388
- NICE NG106. Available at https://www.nice.org.uk/guidance/ng106
- Novartis Pharmaceuticals UK Ltd. Available at: https://www.entrestohcp.com/sfc/servlet.shepherd/version/download/0681H000001rM0cQAE

Development Process

This guidance has been produced following an AMBER classification status of Entresto® by the Barnsley Area Prescribing Committee. This guideline has been subject to consultation and endorsement by the Area Prescribing Committee on 11th November 2020.

Appendix A – Shared Care request form (Amber)

- Specialist to complete when requesting GP to enter a shared care arrangement.
- GP to return signed copy of form.
- Both parties should retain a signed copy of the form in the patient's record.

From (**Specialist**): _____ **To** (**GP**): _____

Patient details

Name: _____ ID Number: _____

Address: _____ DOB: _____

Diagnosed condition: Symptomatic chronic heart failure with reduced ejection fraction

Amber Drug details

Drug name: Sacubitril Valsartan (Entresto®)

Dose and frequency: 24mg/26mg twice daily ☐

49mg/51mg twice daily ☐

97mg/103mg twice daily ☐

Other: _____

Date of initiation: _____ Length of treatment: _____

The patient will be reviewed by the Consultant on: _____

Monitoring

The following monitoring should be undertaken by the GP:

Parameter		**Date last test done**	**Result**	**Date next test due**	**Comments**
BP				Every 6 months, due date =	
U&E's	Na^+			Every 6 months, due date =	
	K^+				
	Creat.				
	Urea				
LFT's	Total Bilirubin (micromol/L)			Once a year, due date =	
	AST (iu/L)				
	ALT (iu/L)				
	GGT (iu/L)				
	ALP (iu/L)				
	Total protein (g/L)				
	Albumin (g/L)				
	Globulin (g/L)				
FBC	Hb (g/L)			Once a year, due date =	
	WCC ($x10^9$/L)				
	Platelets ($x10^9$/L)				
	RBC ($x10^{12}$/L)				
	Haematocrit (L/L)				
	MCV (fl)				
	MCH (pg)				
	MCHC (g/L)				
	RDW				
	Neutrophils ($x10^9$/L)				
	Lymphocytes ($x10^9$/L)				
	Monocytes ($x10^9$/L)				
	Eosinophils ($x10^9$/L)				
	Basophils ($x10^9$/L)				

Communication

Consultant
Telephone number: _____ Fax number:_____

Email address: _____

Specialist Nurse
Telephone number: _____ Fax number: _____

Email address: _____

Specialist (Doctor/Nurse) name: _____

Specialist (Doctor/Nurse) signature: _____ Date: _____

I, Dr ……., can confirm I :

□ accept the request to participate in shared care for the patient named above.

□ reject the request to participate in shared care for the patient named above. The reason for this being
……..

GP signature: _____ Date: _____

To save resources you have been sent appendix A of the shared care document.

The full document (Shared Care Guideline for Entresto® in the management of Chronic Heart Failure, date approved November 2020) can be accessed on the Barnsley BEST website at the following link: http://best.barnsleyccg.nhs.uk/clinical-support/medicines/shared-care-guidelines/

Or via the Barnsley Area Formulary www.barnsleyformulary.nhs.uk