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Implementation of Entresto (Sacubitril/Valsartan) in Dudley Health Economy

For the treatment of symptomatic chronic heart failure with reduced ejection fraction (NICE TA388)

This document is intended as a guideline to give primary care prescribers a clear indication of the reason to initiate a specialist medication, following the request by heart failure specialist service. It is a guideline which suggests criteria for it's subsequent titration, continuation or discontinuation. This guideline should be provided as a supplement to the specialist clinical letter.

The heart failure specialist team will support with the management and subsequent follow up and monitoring in a shared care approach with the GP until the patient is optimised, whereby patient may be discharged from routine heart failure specialist follow up to be transferred to the GP. This will enable patients who are eligible for sacubitril/ Valsartan to receive evidenced based treatment promptly and potentially avoid patient deterioration, hospitalisation and improve their quality of life.

Patient details		**GP details**		**Specialist details**	
Name		**GP name**	Dr	**Specialist name**	
NHS No		**GP address**		**I confirm that this patient is eligible to receive sacubitril valsartan within these defined guidelines**	
DOB					
Patient address				**Signature**	
				Date	
				Contact details	

Rationale for Choice (to be completed by the specialist)

Relevant Diagnosis:	Symptomatic chronic heart failure with reduced ejection fraction (*NICE TA388*)
Reason why sacubitril valsartan has been chosen in preference to drugs without Formulary restrictions:	**Heart failure specialist please check boxes**: Sacubitril with valsartan (Entresto) is recommended 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 (at least 4 weeks as per PARADIGM study) of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor-blockers (ARBs) or, where clinically indicated, can be initiated in patients presenting with heart failure where an ACE inhibitor or ARB has not previously been used. □ • **ACE has been stopped for more than 48 hours (washout period)** □ • Or ARB has been stopped □ • Initiation, dose titration and monitoring should be performed by a member of the specialist heart failure MDT or by the patient's GP, in collaboration with the specialist heart failure MDT □ • Patients with an SBP>100mmHG (treatment initiation is contraindicated at lower SBP) • Patients with a K+<5.4mmol/L (treatment initiation is contraindicated at higher potassium levels) • eGFR>30ml/min. As per NICE NG106, have the following areas been discussed with the patient Lifestyle□ Exercise□ Smoking□ Alcohol□ Salt and fluid restriction □ Sexual activity□ Vaccination□ Air travel□ Driving regulations□

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Pre-treatment test results

Heart failure specialist team to complete the information

Heart failure classification	
Renal function (eGFR- mL/min/1.73 m2)	
Hepatic impairment (Child-Pugh classification)	N/A ☐ A ☐ B ☐ C ☐
Blood pressure (mm/Hg)	
Serum potassium (mmol/L)	
Known history of angioedema / hereditary/ idiopathic angioedema	Yes ☐ No ☐

Pregnancy- contraindicated in second and third trimester of pregnancy

Guidance on initiation *(to be completed by the specialist)*

Initiation dose:	Recommended starting dose : One tablet of 49 mg/51 mg twice daily, except in situations described below. The dose should be doubled at 2-4 weeks to the target dose of one tablet of 97 mg/103 mg twice daily, as tolerated by the patient Treatment should not be initiated in patients with serum potassium level >5.4 mmol/l or with SBP <100 mmHg. A starting dose of 24 mg/26 mg twice daily should be considered for patients with SBP ≥100 to 110 mmHg. From low dose ACEI/ARB or if eGFR 30-60ml/min/1.73m^2 start Entresto 24/26mg (50mg) BD, From high dose ACEI/ARB (and eGFR >60ml/min/1.73m^2) – start 49/51mg (100mg) BD Up-titrate every 2-4 weeks trying to achieve target of 97/103mg (200mg BD), check BP, liver and renal profile at each visit Patient information leaflet to be provided with a named contact person and telephone number in case of any new symptoms/concerns Sacubitril valsartan 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. The valsartan contained within sacubitril valsartan is more bioavailable than the valsartan in other marketed tablet formulations.
Renal impairment	
Mild renal impairment (eGFR 60-90 mL/min/1.73 m2)	No dose adjustment is required
Moderate renal impairment (eGFR 30-60 mL/min/1.73 m2)	A starting dose of 24 mg/26 mg twice daily should be considered
Severe renal impairment (eGFR <30 mL/min/1.73 m2)	Use with caution and a starting dose of 24 mg/26 mg twice daily
End-stage renal disease (dialysis/ pre-dialysis)	Not recommended.
Hepatic impairment	
Mild hepatic impairment (Child-Pugh A classification)	No dose adjustment is required
Moderate hepatic impairment (Child-Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range	Use with caution in these patients and the recommended starting dose is 24 mg/26 mg twice daily
Severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification)	Contraindicated

Specialist recommendations	**Heart failure specialist to complete** The initial introduction and titration should be managed by the heart failure specialist until stable dose and clinical stability is achieved. Limited clinical data and experience in patients with severe NYHA class IV heart failure, who are more likely to suffer from hypotension and renal impairment; these patients should remain under follow up with heart failure specialist. Suggest ACE inhibitor 'wash out' period of 48 hours to minimise risk of angioedema.
Monitoring	See assessment of efficacy below. (frequency to be clarified) • Monitor serum potassium • Monitor renal and hepatic function. • Monitor blood pressure • Monitor for signs of angioedema. • Monitor serum lithium levels if combination with lithium is necessary. • Monitor heart rate if used in combination with sublingual, oral or transdermal nitrates.
Contraindications	Please refer to SPC -Hypersensitivity to the active substances -Concomitant use with ACE inhibitors or ARBs. Entresto must not be administered until ≥ 36 hours after discontinuing ACE inhibitor therapy. -Known history of angioedema related to previous ACE inhibitor or ARB therapy -Hereditary or idiopathic angioedema -Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m^2) -Severe hepatic impairment, biliary cirrhosis and cholestasis -Second and third trimester of pregnancy
Special precautions	Please refer to SPC
Drug Interactions	Important Drug interactions and their management – refer to SPC for further information: **http://www.medicines.org.uk/emc/medicine/31244** Interactions resulting in a contraindication ACE inhibitors Aliskiren Interactions resulting in concomitant use not being recommended Sacubitril/valsartan contains valsartan, and therefore should not be co-administered with another ARB containing medicinal product Interactions requiring precautions OATP1B1 and OATP1B3 substrates, e.g. statins PDE5 inhibitors including sildenafil Potassium Non-steroidal anti-inflammatory agents (NSAIDs), including selective cyclooxygenase-2 (COX-2) inhibitors Lithium Furosemide Nitrates, e.g. nitroglycerine OATP and MRP2 transporters Metformin

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Suggested Criteria for Continuation or Discontinuation (to be completed by the specialist)

Assessment of Efficacy	
Frequency	2-4 weeks initially then annually
Location	Outpatients department/GP practice
Method	Initiation and titration criteria – HF specialist team will provide recommendations to the GP to **prescribe** Entresto / dose from initiation with clear/ concise letter supported by this guidance document HF nurse specialist team will continue to monitor the patient until the dose is optimised and patient is stable Assessment of renal function, hepatic function, blood pressure, serum potassium will be undertaken by HF specialist team until patient is stable. On-going monitoring by GP once stable in line with NICE NG106 Surveillance for signs of angioedema. If combination with lithium necessary, careful monitoring of serum lithium levels. If used in combination with sublingual, oral or transdermal nitrates, monitor heart rate
Continuation Criteria	**Heart failure specialist to complete** Patient will continue to be monitored by HF specialist team until stable. GP will be informed of optimised dose of Entresto to be continued. On-going monitoring by GP once stable in line with NICE NG106. Please add alerts to clinical record to review lifestyle etc. as per NICE NG106
Review	**Heart failure specialist to complete** Heart failure specialist MDT member to review before discharge to primary care, including an assessment of heart failure severity, response to treatment and need for further treatment. Some patients with severe NYHA class IV heart failure may need to continue follow-up due to more limited clinical experience in this patient group and potential for greater adverse events with renal dysfunction and hypotension.
Temporary down-titration or discontinuation criteria	**Discussion with HF specialist team** • Clinically significant hyperkalaemia • Blood pressure - SBP <95mmHg • Deterioration in renal function (eGFR <30 mL/min/1.73 m2) • Adjustment of concomitant medicinal products • Deterioration in hepatic function In the event of hypotension, worsening renal impairment or hyperkalaemia, temporary down-titration of MRA and/or ARNi (review diuretics, MRA, NSAIDs etc.) *(If patients are taking a higher dose of MRA such as spironolactone/Eplerenone the advice would be to reduce the dose of MRA rather than down titrate or stop ARNi.)*
Immediate Discontinuation Criteria	• Angioedema • Increase in serum potassium > 5.4 mmol/L (**Discuss with HF specialist team)** • Breast-feeding • Pregnancy • Severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification)
Follow up action	**Heart failure specialist to complete** Patients with severe NYHA class IV should continue follow up with heart failure specialist.

Additional info	Counselling: sacubitril valsartan may be administered with or without food. The tablets must be swallowed with a glass of water.
Shared Care Read Code	In the patient's notes, using Read Code- 8BM5.00 (shared care prescribing) denote that the patient is receiving treatment under these guidelines
Contact details	dgft.heart-failure-team@nhs.net 01384 323158 (8.00am – 4.00pm- 7 days a week with voicemail option for any out of hours calls)
References	NICE TA 388 - Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction SPC – Sacubitril valsartan (Entresto®) NICE NG106 - Chronic heart failure in adults: diagnosis and management.
Please note the information in this document is correct at the time of writing. **The manufacturer's Summary of Product Characteristics (SPC)** and the most current edition of the **British National Formulary should be consulted for up to date and more detailed prescribing information.**	

Based on BSSE RICaD template

Approved by ACE Jan 2022 **Review date Jan 2024**