

Sacubitril valsartan (Entresto®) for patients with symptomatic chronic heart failure North East and North Central London Position Statement

Sacubitril Valsartan (Entresto®) is licensed for the treatment of symptomatic chronic heart failure in adults with reduced ejection fraction and it can be used in North East and North Central London in line with NICE Technology Appraisal 388 (NICE TA 388).

- Secondary care initiation: Initiation of sacubitril valsartan (Entresto®) is to be undertaken under the direction of a consultant with an established expertise in managing patients with heart failure and access to a multidisciplinary team.
- Primary care initiation: Individual secondary care units may wish to delegate the initiation of sacubitril valsartan to community heart failure teams provided the team has a clinical lead consultant cardiologist and specialist in heart failure who has directly reviewed or had an MDT discussion regarding the patient for treatment options in line with NICE guidance. Community teams should prospectively declare their competence in writing to be able to prescribe sacubitril valsartan or else refer the patient to the consultant to initiate sacubitril valsartan
- Sacubitril valsartan (Entresto®) should not be initiated by a primary care clinician who is not a part of the heart failure multidisciplinary team.
- Continuation: Following titration to optimum tolerated dose, sacubitril valsartan (Entresto®) can be continued in primary care in line with the [“Sacubitril Valsartan \(Entresto®\) for Chronic Heart Failure with Reduced Ejection Fraction” Factsheet](#).
- Key interactions: ACE-inhibitor (ACEi) and/or angiotensin-II receptor blocker (ARBs) should not be used concurrently with sacubitril valsartan (Entresto®). Patients require a minimum of 36 hour wash out from concomitant ACEi and sacubitril valsartan. Review patients’ medication history and discontinue ACEi/ ARBs.

Aim

To support health services in North East and North central London to use sacubitril valsartan (Entresto[®]) in line with NICE TA 388 by:

- Managing patients with chronic heart failure with reduced ejection fraction (HFrEF) in line with NICE guidelines (NG 106) Chronic heart failure in adults: diagnosis and management (September 2018)
- Initiating sacubitril valsartan in a safe, controlled manner where indicated to treat chronic HFrEF.
- Transferring patients who are established on therapy with sacubitril valsartan into primary care with appropriate guidance and support in terms of management and monitoring of the drug and disease.
- Establishing and implementing treatment pathways for initiation, maintenance and monitoring of sacubitril valsartan for chronic HFrEF.

Current pharmacological therapy in treatment of symptomatic chronic heart failure

Pharmacological treatment in patients with HFrEF include as a first line:

- Selective beta-adrenergic receptor antagonists (BB) and an angiotensin converting enzyme inhibitors (ACEi) or angiotensin II receptor blocker (ARB) where ACEi are not tolerated. These are titrated to maximum tolerated evidence based doses (see Appendix 1).
- If patients remain symptomatic and left ventricular ejection fraction (LVEF) <35%, a mineralocorticoid receptor antagonist (MRA) should be added and titrated up to maximum tolerated licensed dose (see Appendix 2).
- Additional agents in those remaining symptomatic are limited. Options include addition of hydralazine and nitrates, digoxin, ivabradine depending on specific patient characteristics.

Other interventions in the treatment of chronic symptomatic heart failure:

- Use of implantable cardioverter defibrillators (ICD) and cardiac resynchronisation therapy (CRT) should be guided as per NICE technology appraisal TA 314 in those with heart failure with a LVEF <35% and additional criteria as summarised in Appendix 2.
- Valve disease, revascularisation and correction of atrial fibrillation or other tachyarrhythmias or withdrawal of cardiotoxic drugs are decisions to be undertaken by the supervising heart failure team prior to being considered for sacubitril valsartan.

Sacubitril valsartan (Entresto[®]) is an option for patients who:

- Meet criteria as defined in NICE TA 388 and NG106 where sacubitril valsartan (Entresto[®]) is an option in those with symptomatic chronic HFrEF who remain symptomatic (NYHA II or above) taking a stable dose of ACEi or ARB and LVEF is <35% .
- Receive the current optimum therapy (as listed above: BB, ACEi or ARB and a MRA titrated to maximum tolerated evidence based doses) a stable period of three months is required without any other pharmacotherapy drug or dose amendment (or withdrawal in the case of cardiotoxic drugs) or other non-pharmacological interventions prior to checking response and changes in ejection fraction. Thereafter, LVEF is to be <35% on echocardiogram or equivalent function on alternative imaging.
- For patients on longstanding therapy, a recent (within 6 months) LVEF is required to be <35%.
- Natriuretic peptides can be used to select patients (as was undertaken in the PARADIGM study) to identify patients who will benefit from treatment with sacubitril valsartan (BNP > 150pg/ml (NT-proBNP>600pg/ml) or if hospitalisation for HF within the last 12 months BNP>100pg/ml (NT-proBNP>400pg/ml). To date there is no large outcome data to support its use in those with natriuretic peptide below those stated.
- A summary of the use of sacubitril valsartan in clinical practice (NG 106) is provided in Appendix 3.

Initiation of sacubitril valsartan

- Initiation of sacubitril valsartan is to be undertaken under the direction of a consultant with an established expertise in managing patients with heart failure and access to a multidisciplinary team. Individual secondary care units may wish to delegate the initiation of sacubitril valsartan to community heart failure teams provided the team has a clinical lead consultant cardiologist and specialist in heart failure who has directly reviewed or had an MDT discussion regarding the patient for treatment options in line with NICE guidance. Community teams should prospectively declare their competence in writing to be able to prescribe sacubitril valsartan or else refer the patient to the consultant to initiate sacubitril valsartan.
- At initiation, patients must be non-pregnant, have systolic BP > 100 mmHg, serum potassium <5.4 mmol/l, eGFR>15 ml/min/1.73 m² (see below for further details regarding dosing in renal impairment), without severe hepatic impairment, biliary cirrhosis and cholestasis. Other exclusion criteria are on the summary of product characteristics.
- For those taking an ACEi, a wash out period of 36 to 48 hours is required, the exact duration determined by patient's current therapy and clinical characteristics. This is to reduce increased risk of severe angioedema with concomitant ACEi and sacubitril use.
- For those taking an ARB, start sacubitril valsartan at next scheduled dose of ARB.
- Initiation and titration to stable maintenance dose should be undertaken by the initiating team, it is estimated this may take up to 3 months in selected patients as although tolerability was similar to ACEi in the PARADIGM trial, this was undertaken in highly selected patients that the group felt were relatively more stable than those generally seen in clinic.
- Starting dose and titration in those on established ACEi or ARB (after ceasing ACEi or ARB):
 - Initiate 49mg/51mg sacubitril valsartan twice daily for 2-4 weeks then
 - Increase to 97mg/103mg sacubitril valsartan twice daily thereafter
- Starting dose in those patients not taking an ACEi or ARB, or taking low doses:
 - Initiate 24mg/26mg sacubitril valsartan twice daily for 3-4 weeks then
 - Increase to 49mg/51mg sacubitril valsartan twice daily for 3-4 weeks then
 - Increase to 97mg/103mg sacubitril valsartan twice daily thereafter
- If patients experience tolerability issues (systolic blood pressure ≤95 mmHg, symptomatic hypotension, hyperkalaemia, renal dysfunction), adjustment of concomitant medicinal products, temporary down-titration or discontinuation is recommended). NOTE: Full details of side effects and monitoring parameters can be found in the summary of product characteristics available at www.medicines.org.uk
- It is encouraged to follow up outcomes in patients newly started on sacubitril valsartan. Depending on resources available this could be undertaken locally or collectively using a registry data base ideally supported by academic health science network.

Dosing in renal impairment

- Mild renal impairment (eGFR 60-90mL/min/1.73m²): No dose adjustment is required.
- Moderate renal impairment (eGFR 30-60 mL/min/1.73m²): A starting dose of 24mg/26mg twice daily should be considered.
- Severe renal impairment (eGFR 15-30 mL/min/1.73m²): There is limited clinical experience in patients with severe renal impairment and as such should be used with caution and a starting dose of 24mg/26mg twice daily is recommended.
- End-stage renal disease (eGFR<15mL/min/1.73m²): There is no experience in patients with end-stage renal disease and use of sacubitril valsartan is not recommended.

Maintenance and transfer to primary care

- Following titration to optimum tolerated dose, maintenance will be continued in primary care.
- Ongoing monitoring of urea and electrolytes (as in NICE NG 106) every 6 months should be sufficient to monitor renal effects of sacubitril valsartan.
- A [factsheet](#) has been prepared to support primary care practitioners in prescribing sacubitril valsartan and will facilitate a seamless transition to primary care.
- CCG commissioned community heart failure services would be expected to play a key role in facilitating an integrated care approach, in accordance with local guidelines.

Patient support

- There should be an amnesty to encourage patients to bring all ACEi and ARB to clinic/pharmacy for destruction to prevent inadvertent consumption while taking sacubitril valsartan
- Novartis has developed a wallet sized cards for patients to carry that can be shown to health care professionals to alert them to the interactions of sacubitril valsartan and ACEi.

References

1. Chronic heart failure in adults: Diagnosis and management. NICE guideline 106 (September 2018).
2. Ivabradine for treating chronic heart failure. NICE technology appraisal guidance no. 267 (2012).
3. Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure. NICE technology appraisal guidance no. 314 (2014).
4. Insertion and use of implantable pulmonary artery pressure monitors in chronic heart failure. NICE interventional procedure guidance 463 (2013).
5. Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction. NICE technology appraisal guidance no. 388 (2016).
6. Ponikowski P, Voors AA, Anker SD et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, available at doi:10.1093/eurheartj/ehw128.
7. McMurray JJV, Packer M, Desai AS et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Eng J Med 2014; 371:993-1005.

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Appendix 1: Optimum doses of selected pharmacotherapy used in heart failure

	Starting dose	Target dose
ACEi		
Captopril	6.25mg bd - tds	50mg tds
Enalapril	2.5mg bd	20mg bd
Lisinopril	2.5-5mg od	35mg od
Ramipril	2.5mg od	10mg od (preferably in divided doses)

	Starting dose	Target dose
ARB		
Candesartan	4mg od	32mg od
Losartan	25mg od	150mg od
Valsartan	40mg bd	160mg bd

	Starting dose	Target dose
MRA		
Eplerenone	25mg od	50mg od
Spirolactone	25mg od	50mg od

	Starting dose	Target dose
BB		
Bisoprolol	1.25mg od	10mg od
Carvidolol	3.125mg bd	25mg bd

Adapted from ESC guidance 2016 and UK license

Appendix 2: Current device recommendations (NICE TA 314 summary table)

QRS interval	NYHA class			
	I	II	III	IV
<120 milliseconds	ICD if there is a high risk of sudden cardiac death			ICD and CRT not clinically indicated
120–149 milliseconds without LBBB	ICD	ICD	ICD	CRT-P
120–149 milliseconds with LBBB	ICD	CRT-D	CRT-P or CRT-D	CRT-P
≥150 milliseconds with or without LBBB	CRT-D	CRT-D	CRT-P or CRT-D	CRT-P
LBBB, left bundle branch block; NYHA, New York Heart Association				

Appendix 3: NICE NG 106 Treatment algorithm for Heart failure

