North East and North Central London Position statement:

Introduction of sacubitril valsartan (Entresto®) for patients with symptomatic chronic heart failure for the period June 2016 to June 2017.

Aim:

To support health services within the defined geographical region to:

- Initiate, in a safe and controlled manner the introduction of a new class of drug in the treatment of chronic heart failure with reduced ejection fraction (HFrEF).
- Determine how patients established on therapy with sacubitril valsartan are transferred and appropriately monitored in secondary care.
- Establish clear treatment pathways for initiation, maintenance and monitoring of this first in class treatment for chronic HFrEF.
- Review position statement after 12 months of sacubitril valsartan introduction to act on experience and continuing evidence base.

Current standard pharmacological therapy in treatment of symptomatic chronic heart failure (prior to sacubitril valsartan):

- 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) $\leq$35%, a mineralocorticoid receptor antagonist (MRA) should be added and titrated up to maximum tolerated licenced dose (see appendix 1).
- 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 $\leq$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, a new treatment option:

- In line with NICE TA 388, sacubitril valsartan is an option in those with symptomatic chronic HFrEF in those who remain symptomatic (NYHA II or above) taking a stable dose of ACEi or ARB and LVEF is $\leq$35%
- To determine full treatment effect of 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%.
- For the purpose of the next 12 months, we recommend the use of natriuretic peptides 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.

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.
- For patients in primary care identified as candidates for sacubitril valsartan, referral to cardiology specialist is recommended in order to undertake baseline assessment and investigations.
- At initiation, patients must be non-pregnant, have systolic BP > 100 mmHg, serum potassium <5.4 mmol/l, eGFR>30 ml/min/1.73 m2 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.

Maintenance and transfer to primary care

- Following titration to optimum tolerated dose, maintenance will be continued in primary care.
- Ongoing monitoring of U&Es (as in NICE CG 108) every 6 months should be sufficient to monitor renal effects of sacubitril valsartan.
- A transfer of care document and FACT sheet have been prepared to support general practitioners in prescribing sacubitril valsartan and will facilitate a seamless transition to primary care.

Patient support and information

- A patient information leaflet (appendix 4) can be offered to patients to support treatment initiation of sacubitril valsartan therapy. Additionally, it will detail instructions to avoid concomitant ACEi and confirm advice for patients during sick days.
- 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:

- Chronic heart failure: Management of chronic heart failure in adults in primary and secondary care. NICE clinical guideline 108 (2010)
- Ivabradine for treating chronic heart failure. NICE technology appraisal guidance no. 267 (2012)
- Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure. NICE technology appraisal guidance no. 314 (2014)
- Insertion and use of implantable pulmonary artery pressure monitors in chronic heart failure. NICE interventional procedure guidance 463 (2013).
- Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction. NICE technology appraisal guidance no. 388 (2016)
- 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
- 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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Declaration of interests:

A.Barron payment by Novartis to provide staff training on the pre-NICE Budget Impact Model, A.Bakhai recruit to trials sponsored by pharma, device and diagnostics companies and advise on clinical trial design, analyses and health economic modelling including Novartis. Advisory and educational roles on improving the care of patients with reduced cardiac output also for Novartis, Roche, Bayer, Pfizer, Medtronic, NICE, Oxford outcomes, HealthXL and Amore Health. S.Antoniou Received honoraria from Novartis. C.Davis - Research funding and sponsorship from Novartis for attendance to ESC-HF meeting

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

(Adapted from ESC guidance 2016 and UK license)

	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
MRA		
Eplerenone	25mg od	50mg od
Spironolactone	25mg od	50mg od

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

	Starting dose	Target dose
BB		
Bisoprolol	1.25mg od	10mg od
Carvidolol	3.125 bd	25mg bd
Nebivolol	12.5mg od	10mg od

Appendix 2 – Current device recommendations (summary table)

(Taken from NICE TA 314)

	NYHA class			
QRS interval	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 – Position statement – Use of sacubitril valsartan in clinical practice