

Sacubitril valsartan (Entresto®) for patients with symptomatic chronic heart failure

North East and North Central London Position statement 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) <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 <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 <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.
- A summary of the use of sacubitril valsartan in clinical practice 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.
- 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 urea and electrolytes (as in NICE CG 108) every 6 months should be sufficient to monitor renal effects of sacubitril valsartan.
- A transfer of care document and Factsheet have 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 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

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- 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-nepriylsin inhibition versus enalapril in heart failure. N Eng J Med 2014; 371:993-1005.

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Declaration of interests

S Antoniou received honoraria from Novartis. A Barron received payment by Novartis to provide staff training on the pre-NICE Budget Impact Model. Dr 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. Dr C Davis received research funding and sponsorship from Novartis for attendance to ESC-HF meeting. Dr C Whelan received sponsorship

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

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

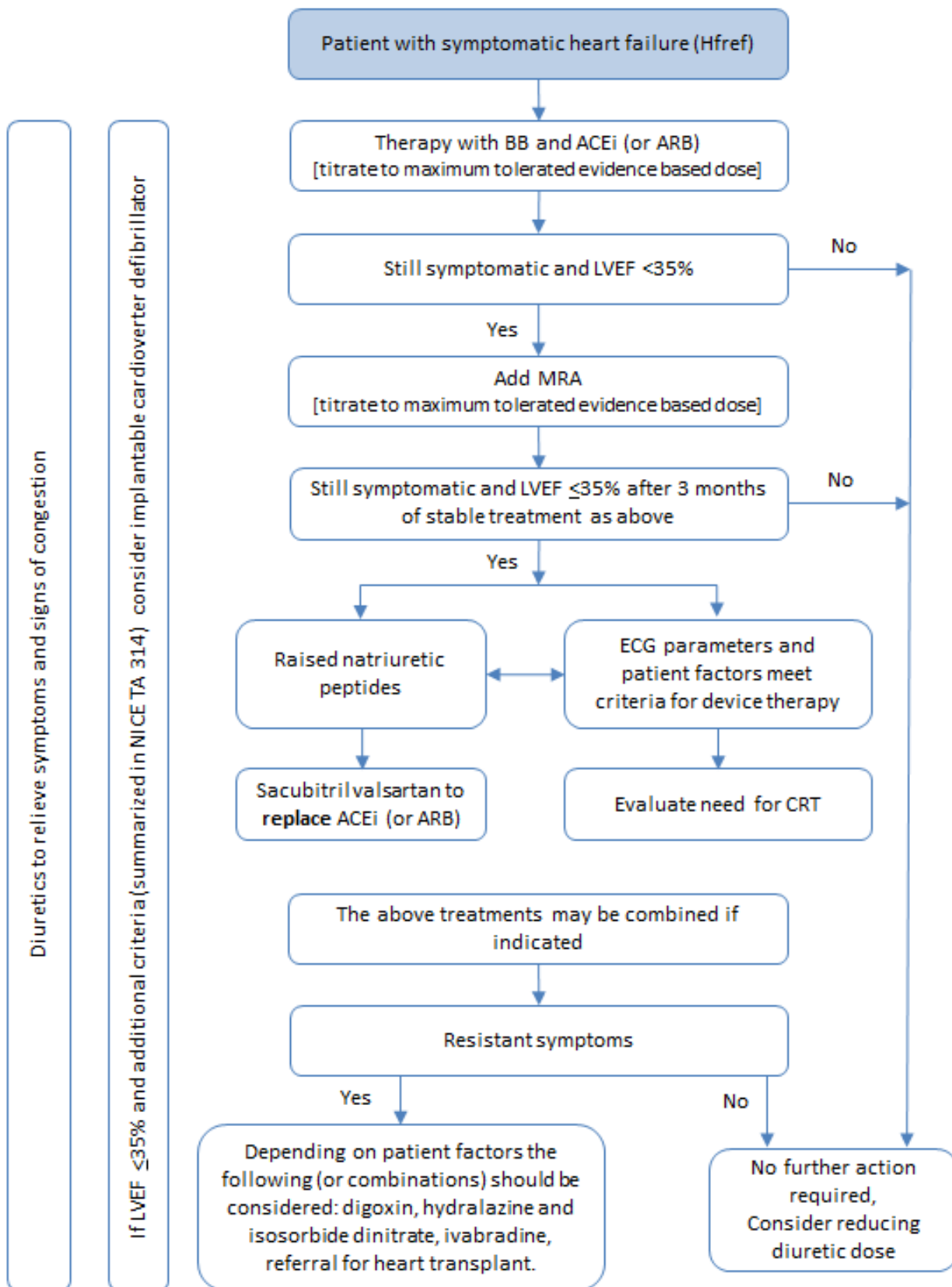
	Starting dose	Target dose
BB		
Bisoprolol	1.25mg od	10mg od
Carvidolol	3.125mg bd	25mg bd
Nebivolol	12.5mg od	10mg od

Appendix 2: Current device recommendations (summary table)

Taken from NICE TA 314

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: Position statement – Use of sacubitril valsartan in clinical practice



Patient information for those starting on sacubitril valsartan (Entresto®)

What is sacubitril valsartan (Entresto®)?

Your clinician has recommended a new treatment for you to reduce the risk of death and hospitalisation in people with certain types of long-lasting (chronic) heart failure. This treatment is used with other heart failure therapies and will replace an ACE inhibitor (such as ramipril or lisinopril) or an ARB therapy (such as candesartan or losartan). The generic name for the drug is sacubitril valsartan while the branded name is Entresto®, for the purpose of this leaflet the brand name will be used throughout.

Are there side effects of treatment?

Like all medicines, Entresto® can cause side effects although not everybody gets them. In a large clinical trial comparing Entresto® to an ACE inhibitor, patients in both groups suffered in equal numbers to common side effects as listed below (this is not a complete list but highlights the main side effects):

Very common (may affect more than 1 in 10 people):

- low blood pressure (dizziness, light-headedness)
- high level of potassium in the blood (shown in a blood test)
- decreased kidney function (kidney impairment)

Common (may affect up to 1 in 10 people):

- cough
- feeling sick (nausea)
- headache
- dizziness, fainting
- spinning sensation
- tiredness, weakness
- diarrhoea
- inflammation of the lining of the stomach (stomach pain, nausea)
- (acute) kidney failure (severe kidney disorder)

Uncommon (may affect up to 1 in 100 people):

- allergic reaction with rash and itching
- dizziness when switching from sitting to standing position

May be serious.

- Stop taking Entresto® and seek immediate medical attention if you notice swelling of the face, lips, tongue and/or throat, which may cause difficulties in breathing or swallowing. These may be signs of angioedema (an uncommon side effect which may affect up to 1 in 100 people).
- British-Caribbean, British-African or African, Caribbean and take Entresto® may have a higher risk of having angioedema than people who are not Black and take Entresto®, although the risk still remains relatively small affecting up to 1 in 100 people.

There may be a theoretical increased risk of Alzheimer's disease. There is on-going research into this area. In the most recent trial this was not seen but please be aware it was a short trial and further research needs to take place to confirm whether or not there is a risk.

How do I take Entresto®?

The starting dose will be determined by a number of factors but you will usually start on a lower dose which will be adjusted depending on how you respond to treatment until the best dose is found for you. The tablet is taken twice a day (once in the morning and again in the evening). It should be taken with a small glass of water and can be taken with or without food. It is advisable to take your medicine at the same time each day. Should you forget to take a dose, you should simply take the next one at the scheduled time. Do not take a double dose to make up for a forgotten tablet.

What if I am pregnant or planning to have a family?

You must inform your doctor if you think that you are (or might become) pregnant. Your doctor will normally advise you to stop taking this medicine before you become pregnant or as soon as you know you are pregnant, and will advise you to take another medicine instead of Entresto®. This medicine is not recommended during pregnancy as it may cause serious harm to your baby. Additionally Entresto® is not recommended for mothers who are breastfeeding. Tell your doctor if you are breastfeeding or about to start breastfeeding.

Can I drive and/or use machinery while taking Entresto®

Before you drive a vehicle, use tools or operate machines, or carry out other activities that require concentration, make sure you know how Entresto® affects you. If you feel dizzy or very tired while taking this medicine, do not drive a vehicle, cycle or use any tools or machines.

Other important information

It is important that you DO NOT take an ACE inhibitor or an ARB at the same time as Entresto®. Your doctor will advise you to start Entresto® **at least 36 hours before or after you take an ACE inhibitor medicine**. Talk with your doctor or pharmacist before taking Entresto® if you are not sure if you take an ACE inhibitor medicine. It is advisable that you take any remaining ACE inhibitors or ARBs to your chemist for destruction if you are starting Entresto®, if you are unsure then ask your doctor or pharmacist and they can point out which ones these are.

Should I stop my tablets if I'm suffering from diarrhoea and/or sickness during treatment?

Should you suffer from a brief bout of diarrhoea or sickness (less than 2 days), it is recommended from your heart failure team to keep taking your medication. Should you become dehydrated or the illness lasts longer than 2 days without improving, you should seek advice from your heart failure team or GP on whether to continue taking this and other heart failure medication. Depending on your symptoms a blood test to check your kidney function may be requested prior to making a decision.

Patient alert card

The company have developed a "patient alert card" that will be given to you with your first prescription and should be kept with you at all times. The card alerts other health care professionals about the serious interaction between Entresto® and ACE inhibitors and a reminder that it ***should not be prescribed with either ACEi or ARBs***.

If you have any other questions about starting Entresto®, please be sure to ask your doctor prior to starting treatment.