Somerset Healthcare Community
Shared Care Protocol

NHS
Somerset
Clinical Commissioning Group

Sacubitril valsartan for the treatment of chronic heart failure

This shared care protocol (SCP) sets out details for the sharing of care for patients requiring sacubitril valsartan (Entresto™). It should be read in conjunction with the Summary of Products Characteristics (SPC, available at http://www.medicines.org.uk/emc)

As outlined in NHS Circular 1992 (Gen 11), when a consultant considers a patients' condition is stable he/she may seek the agreement of the patients' GP to "share" the patients' care. This document provides information on drug treatment for the shared commitment between the consultant and GP concerned. GPs are invited to participate. If the GP is not confident to undertake these roles, then they are under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. The doctor who prescribes the medication has the clinical responsibility for the drug and the consequences of its use.

Introduction

Sacubitril valsartan (Entresto™) contains a salt complex of valsartan and the first in class neprilysin inhibitor sacubitril.

It has shown to be of benefit in patients with heart failure secondary to left systolic dysfunction.

The Phase III trial which demonstrated its benefits over ACE inhibitors was published in the New England Journal of Medicine in 2014. This trial was stopped early because of 'overwhelming benefit' There was a clinically significant reduction in all-cause mortality, hospitalization and symptoms.

It will be prescribed by Cardiology, Heart Failure teams and general practitioners.

For further information, please click on the links below or visit;
British National Formulary
Summary of Product Characteristics
SIGN Chronic Heart Failure Booklet

Nice Approval (TA 388)

Entresto™ is recommended in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction, but only in people:

- With NYHA class II to IV chronic heart failure and
- Who are already taking a stable dose of ACE inhibitor or ARBs and

- With a left ventricular ejection fraction of 35% or less.

Dose (posology & method of administration)

Adults: Initially one 49mg/51mg tab twice daily, increasing after 2—4 weeks if tolerated to one 97mg/103mg tab twice daily.

Patients taking no or low-dose ACE inhibitor or angiotensin II antagonist, initially 24mg/26mg twice daily, doubling dose every 3—4 weeks to one 97mg/103mg tab twice daily.

Dose reduction is required in moderate renal impairment (eGFR 30-60ml/min). Avoid in severe impairment (eGFR < 30ml/min).
There is limited clinical experience in patients with moderate hepatic impairment.

If patients experience tolerability issues (systolic blood pressure [SBP] ≤95 mmHg, symptomatic hypotension, hyperkalaemia, renal dysfunction), adjustment of concomitant medicinal products, or temporary down–titration or discontinuation of Entresto™ is recommended.

Contra-indications (click for details in SPC)

- Concomitant use within 48 hours of ACE inhibitors
- Concomitant use with ARBs
- Concomitant use with aliskiren
- Serum potassium > 5.4mmol/L
- End stage renal disease.
- Systolic BP < 100mgHg.
- History of angioedema related to previous ACE inhibitor or ARB therapy.
- Hereditary or idiopathic angioedema.
- Severe hepatic impairment, biliary cirrhosis or cholestasis.
- Second and third trimester of pregnancy.
- Lactation.

Special warnings and precautions for use (click for details in SPC)

- Treatment should not be initiated unless SBP is ≥100 mmHg.
- Correct sodium and volume depletion before starting treatment and monitor BP during initiation and dose titration.
- Monitor serum potassium.
- Moderate to severe renal impairment (CrCl <60ml/min).
- Renal artery stenosis; monitor renal function.
- Consider dose reduction if hypotension, hyperkalaemia or renal impairment occurs.
- Moderate hepatic impairment.
- History of angioedema, black patients. NYHA class IV heart failure.

Interactions (click for details in SPC)

- ACE inhibitors.
- Aliskiren.
- Angiotensin II antagonists...
- NSAIDs.
- Inhibitors or substrates of OATP1B1 or OATP1B3 (e.g. statins).
- Inhibitors of OAT1 (e.g. tenofovir, cidofovir).
- Inhibitors of OAT3 (e.g. rifampicin, ciclosporin).
- Inhibitors of MRP2 (e.g. ritonavir).
- Inhibitors of PDE5 (e.g. sildenafil).
- Potassium supplements.
- Potassium-sparing diuretics.
- Aldosterone antagonists.
- Potassium – concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other agents (such as heparin) may lead to increases in serum potassium, and to increases in serum creatinine. Monitoring of serum potassium is recommended if co-administered with these agents.
- Lithium.

MHRA Drug Safety Update**;** use of medicines from different classes of renin-angiotensin system blocking agents: risk of hyperkalaemia, hypotension, and impaired renal function—new warnings

- Combination use of medicines from two classes of RAS blocking agents (ACE-inhibitors, ARBs, or aliskiren) is not recommended.
- In particular, prescribers are advised not to give patients with diabetic nephropathy an ACE-inhibitor with an ARB since they are particularly prone to developing hyperkalaemia.
- The combination of aliskiren with an ACE-inhibitor or ARB is contraindicated in patients with kidney impairment or diabetes.

Pregnancy and Lactation (click for details in SPC)

- Not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy.
- Not recommended during breast-feeding.

Adverse effects (click for details in SPC)

- Hypotension, hyperkalaemia and renal impairment (≥1/10).
- Headache, dizziness, syncope, cough, GI upset, hypokalaemia, hypoglycaemia, anaemia, fatigue, asthenia vertigo (≥1/100 to <1/10).
- Angioedema (≥1/1,000 to <1/100) - discontinue immediately.

Shared Care Responsibilities

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care should be explained to, and accepted by, the patient. This provides an opportunity to discuss drug therapy.

The clinician who prescribes the medication has the clinical responsibility for the drug and the consequences of its use.

Specialist responsibilities: -

1. Consultant cardiologist to assess the need for sacubitril valsartan (Entresto™).
2. When initiating treatment give counselling in verbal and written form.
3. Complete relevant baseline investigations if commencing sacubitril valsartan treatment.
4. Assess for sodium and/or volume depletion and ensure that any depletion is corrected before starting treatment.
5. Check that serum potassium level is <5.4 mmol/L before starting treatment.
6. Stop ACE inhibitors – do not start treatment with sacubitril valsartan until at least 48 hours after taking the last dose of ACE inhibitor therapy. ARBs should also be stopped.
7. If angioedema occurs, sacubitril valsartan should be immediately discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred
8. Follow the patient's response to treatment at the out-patient clinic.
9. Communicate advice to the patient's GP regarding monitoring requirements.
10. Issue prescriptions until the patient is on a stable dose and supervise monitoring to be followed up by the heart failure team.
11. Once stabilised on an appropriate dose request GP to continue/commence monitoring
12. Request GP to monitor as required in the monitoring section of this protocol.
13. Advise GP regarding any concerns about monitoring or adverse effects at any stage.
14. To exercise caution when initiating sacubitril valsartan in patients with impaired renal function.

Consultant monitoring

For patients commencing treatment with sacubitril valsartan

FBC, U&E (eGFR), LFTs, BP prior to treatment
FBC, U&E (eGFR) every 2 weeks after starting treatment or after any dose titration
Blood pressure every 2 weeks after starting treatment or after any dose titration

General Practitioner responsibilities: -

1. Prescribe the appropriate dose under the shared care of the hospital consultant.
2. Monitor the general health of the patient and as detailed in the 'Monitoring' section.
3. Do not co-prescribe ACE inhibitors or ARBs
4. Withold treatment with sacubitril valsartan if eGFR <30 ml/min/1.73m2 due to increased risk of toxicity. Before re-initiating treatment seek advice from specialist if eGFR remains < <30 ml/min/1.73m^2).
5. If serum potassium level is >5.4 mmol/l discontinuation should be considered.

6. Monitor blood pressure routinely. If hypotension occurs, adjustment of concomitant medicinal products or temporary down–titration or discontinuation of Entresto™ is recommended. **Seek specialist advice.**
7. If angioedema occurs, sacubitril valsartan should be immediately discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred.
8. Discuss any important test abnormality with the specialist before continuing treatment
9. Ensure that the patient has received counselling in verbal and written form.
10. Report any suspected adverse reactions to the hospital.
11. Report any significant events relating to sacubitril valsartan therapy to the CCG and via the yellow card route.
12. Liaise with the hospital consultant regarding any complications of treatment

General Practitioner monitoring

Stable patients

FBC, U&E **(eGFR)**, BP: every 3 months for 9 months, then every 6 months.

Following dose titration

FBC, U&E **(eGFR)**, BP every 2 weeks until stable.

Monitoring action and advice for the GP

WITHOLD SACUBITRIL VALSARTAN and contact consultant if:

- Serum potassium >5.4 moll/L
- E-GFR <30 ml/min/1.73m$^{2.}$
- Systolic BP <100 mmHg

If patients experience tolerability issues (systolic blood pressure [SBP] ≤95 mmHg, symptomatic hypotension, hyperkalaemia, renal dysfunction), adjustment of concomitant medicinal products or temporary down–titration or discontinuation of Entresto™ is recommended. **Seek specialist advice.**

Note: a rapid up or down trend in any values should prompt caution and extra vigilance.

Patient/carer responsibilities

1. After counselling, to be willing to administer the sacubitril valsartan as directed at home.
2. Read the patient information leaflet.
3. Be aware that taking OTC aspirin and NSAIDs in addition (e.g. ibuprofen, naproxen) to sacubitril valsartan may interfere with treatment.
4. Report any other medication being taken, including over-the-counter products.
5. Report any adverse effects or warning symptoms whilst taking sacubitril valsartan.
6. Report any concerns in relation to treatment with your doctor.

If a dose is missed, take the next dose at the scheduled time

Drug cost
MIMS, March 2016

Formulation	Dose and pack size	Dose	Cost per 14 days	Cost per 28 days
Entresto™ tablets	24mg/26mg	24mg/26mg bd	£45.78	
	49mg/51mg	49mg/51mg bd	£45.78	£91.56
	97mg/103mg	97mg/103mg bd		£91.56

Further support
- Medicines Information department, Musgrove Park Hospital: 01823 342253
- Medicines Information department, Yeovil District Hospital: 01935 384327
- Prescribing & Medicines Management Team, NHS Somerset CCG: 01935 384123

Version:	1.1	Date
Drawn up by:	Version 1.1 by Nigel Ankcorn, Lead Pharmacist, MI, Musgrove Park Hospital	June2016
Approved by:	Somerset Prescribing Forum, NHS Somerset	July 2016
	Drug & Therapeutics Committee, Taunton & Somerset NHS FT	July 2016
	Drug & Therapeutics Committee, East Somerset NHS FT	July 2016
	Drug & Therapeutics Committee, Somerset Partnership NHS FT	July 2016
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References

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- NICE TA 388 https://www.nice.org.uk/guidance/ta388/resources/sacubitril-valsartan-for-treating-symptomatic-chronic-heart-failure-with-reduced-ejection-fraction-82602856425157