NORFOLK AND WAVENEY STP THERAPEUTICS ADVISORY GROUP (TAG)

SHARED CARE AGREEMENT

Shared care guidelines for Use of Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction

Monitoring Level 1 - Prescribe the drug and perform a higher level of monitoring e.g. 6 monthly

Generic and Proprietary/Brand Name

Sacubitril Valsartan / Entresto®

Indications for shared care

For treating symptomatic chronic heart failure with reduced ejection fraction

Specialist Prescribing and Monitoring Responsibilities – summary. Full details in main body of document	GP / Community Team - Primary Care Prescribing and Monitoring Responsibilities – summary. Full details in main body of document
Prescribing: • Initiate and stabilise treatment before GP transfer • To provide the GP with appropriate information • To be available for advice if patient's condition changes • To advise the GP of any dosage adjustments, monitoring, when to refer back and when and how to stop treatment • To ensure that procedures are in place for rapid re-referral of the patient by the GP • To monitor the patient at six monthly intervals. • To monitor the patient for adverse events and report to the GP and where appropriate Commission on Human Medicines/MHRA (Yellow card scheme). **Monitoring:** • Renal function • Serum potassium • Blood pressure	**Prescribing:** • Initially refer patient for specialist advice • Continue to prescribe sacubitril valsartan as part of a shared care arrangement, at least 4 weeks after treatment has been initiated • Ensure there are no interactions with any other medications. • To refer back to the specialist where appropriate. • To monitor concordance with therapy and raise concerns with the specialist team as appropriate. • Discontinue the drug as directed by the specialist • To identify adverse events and liaise with the hospital specialist • To report adverse events to the specialist and where appropriate the Commission on Human Medicines/MHRA (Yellow card scheme). **Monitoring:** • Renal function and electrolytes every six months and more often during periods of illness • Consider referral where any significant decrease in renal function is noted • Record blood pressure and heart failure symptoms

Patient Information

The Patient Information Leaflet for *Entresto*® should be provided to the patient at the point of dispensing.

Specialist Contact Details

QEH
Dr Nata, Dr Bilku and Dr Petch (Secretary): Tel 01553 613610
Dr Felix, Dr Mohammad, Dr West/Calvert and Dr Heck (secretary): Tel 01553 613781

NNUH:
Dr Ryding: Tel 01603 287690
Dr Grahame-Clarke: Tel 01603 287516
Dr Sunil Nair: Tel 01603 287885

GENERAL PRINCIPLES FOR SHARED CARE PRESCRIBING

- Shared Care is only appropriate if it provides the optimum solution for the patient.
- GPs are **invited** to participate. If GPs are not confident to undertake these roles, 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.
- **If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable if they are unwilling to do so.**
- Prescribing responsibility will only be transferred when it is agreed by the consultant and the patient's GP and when the patient's condition is stable or predictable.
- Safe prescribing must be accompanied by effective monitoring.
- **The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.**

Background to Treatment

Entresto® (Sacubitril valsartan) is an angiotensin receptor neprilysin inhibitor, including both a neprilysin inhibitor (sacubitril) and an angiotensin II receptor blocker (ARB; valsartan).

Entresto® exhibits the mechanism of action of an angiotensin receptor neprilysin inhibitor by simultaneously inhibiting neprilysin (neutral endopeptidase; NEP) and by blocking the angiotensin II type-1 (AT1) receptor via valsartan.

The treatment's complementary cardiovascular benefits in heart failure patients are attributed to the enhancement of peptides that are degraded by neprilysin, such as natriuretic peptides (NP), by LBQ657 and the simultaneous inhibition of the effects of angiotensin II by valsartan.

NPIs exert their effects by activating membrane-bound guanylyl cyclase-coupled receptors, resulting in increased concentrations of the second messenger cyclic guanosine monophosphate (cGMP), which could result in vasodilation, natriuresis and diuresis, increased glomerular filtration rate and renal blood flow, inhibition of renin and aldosterone release, reduction of sympathetic activity, and anti-hypertrophic and anti-fibrotic effects.

Valsartan inhibits detrimental cardiovascular and renal effects of angiotensin II by selectively blocking the AT1 receptor, and also inhibits angiotensin II-dependent aldosterone release. This prevents sustained activation of the renin-angiotensin-aldosterone system that would result in vasoconstriction, renal sodium and fluid retention, activation of cellular growth and proliferation, and subsequent maladaptive cardiovascular remodelling.

Licensed use and agreed local off-label use

Entresto® (Sacubitril valsartan) is licensed for use in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.

Criteria for Patient Selection

NICE TA 388 states that sacubitril valsartan 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 of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor-blockers (ARBs).

Treatment with sacubitril valsartan should be started by a heart failure specialist with access to a multidisciplinary heart failure team. Dose titration and monitoring should be performed by the most appropriate team member as defined in NICE's guideline on chronic heart failure in adults: management.

Locally it is expected that initiation and up-titration be done under the direct supervision of a consultant cardiologist (between 1 and 3 months). Once stabilised on treatment, the responsibility for continued prescription of sacubitril valsartan (*Entresto*®) would pass to the patient's GP.

Treatment will be discontinued if there is evidence of futility (e.g. end of life), end stage renal failure or an adverse reaction.

Form and strength of preparation

- 24mg / 26mg film-coated tablets
- 49mg / 51mg film-coated tablets
- 97mg / 103mg film-coated tablets

Side Effects and Management

Link to BNF

Link to SPC

Very common (≥ 1 in 10)

- Hyperkalaemia
- Hypotension
- Renal impairment

Common (≥ 1 in 100 and < 1 in 10)

- Anaemia
- Hypoglycaemia
- Headache
- Vertigo
- Cough
- Nausea
- Renal failure (renal failure, acute renal failure)
- Hypokalaemia
- Dizziness
- Syncope
- Orthostatic hypotension
- Diarrhoea
- Gastritis
- Fatigue
- Asthenia

Uncommon (≥ 1 in 1000 and < 1 in 100)

- Hypersensitivity
- Pruritus
- Angioedema
- Dizziness postural
- Rash

Drug Interactions

Link to BNF

Link to SPC

The following drugs are contraindicated with sacubitril valsartan**:**

- ACE inhibitor-containing products
- Aliskiren
- ARB containing products

Whilst not contra-indicated for co-administration, the following require *caution*:

Sacubitril valsartan may increase the systemic exposure to **statins**. No formal recommendations exist on management of the combination however sensible precautions would include patients being reminded to report symptoms such as muscle pains and for liver function tests to be performed as part of any routine checks alongside renal function etc.

Concomitant use of **potassium-sparing diuretics** (triamterene, amiloride), **mineralocorticoid antagonists** (e.g. spironolactone, eplerenone), **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 sacubitril valsartan is co-administered with these agents.

In elderly patients, volume-depleted patients (including those on diuretic therapy), or patients with compromised renal function, concomitant use of *Entresto*® and **NSAIDs** may lead to an increased risk of worsening of renal function. Therefore, monitoring of renal function is recommended when initiating or modifying treatment in patients on *Entresto*® who are taking NSAIDs concomitantly.

Sacubitril valsartan taken with sildenafil is associated with significantly greater blood pressure reduction compared to administration of sacubitril valsartan alone. Therefore, caution should be exercised when **sildenafil or another PDE5 inhibitor** is initiated in patients treated with sacubitril valsartan (and vice versa).

Co-administration of sacubitril valsartan with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. **rifampicin, ciclosporin**), OAT1 (e.g. **tenofovir, cidofovir**) or MRP2 (**e.g. ritonavir**) may increase the systemic exposure of the active metabolite of sacubitril (LBQ657) or valsartan.

Co-administration of sacubitril valsartan with **metformin** reduced both Cmax and AUC of metformin by 23%. The clinical relevance of these findings is unknown. Therefore, when initiating therapy with sacubitril valsartan in patients receiving metformin, the clinical status of the patient should be evaluated.

Reversible increases in serum **lithium** concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or angiotensin II receptor antagonists. Interactions between sacubitril valsartan and lithium have not been investigated. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased further.

Cautions and Contraindications

Link to BNF

Link to SPC

Contraindications:

- Treatment should not be initiated in patients with serum potassium level >5.4 mmol/l or with SBP <100 mmHg
- End stage renal failure
- Sacubitril valsartan (*Entresto*®) should ***not*** be co-administered with an ACE inhibitor or an ARB.
- Hypersensitivity to the active substances or to any of the excipients.
- 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 m2).
- Severe hepatic impairment, biliary cirrhosis and cholestasis.
- Second and third trimester of pregnancy

Cautions:

The valsartan in *Entresto*® is more bioavailable than in other marketed tablet formulations.

If hypotension occurs, temporary down-titration or discontinuation of *Entresto*® is recommended. Dose adjustment of diuretics, concomitant anti-hypertensives and treatment of other causes of hypotension (e.g. hypovolaemia) should be considered. Symptomatic hypotension is more likely to occur if the patient has been volume-depleted, e.g. by diuretic therapy, dietary salt restriction, diarrhoea or vomiting.

Sodium and/or volume depletion should be corrected before starting treatment with *Entresto*®, however, such corrective action must be carefully weighed against the risk of volume overload.

No dose adjustment is required in patients with mild (Estimated Glomerular Filtration Rate [eGFR] 60-90 ml/min/1.73 m^2) renal impairment.

A starting dose of 24 mg/26 mg twice daily should be considered in patients with moderate renal impairment (eGFR 30-60 ml/min/1.73 m^2).

As there is very limited clinical experience in patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) sacubitril valsartan should be used with caution and a starting dose of 24 mg/26 mg twice daily is recommended.

There is no experience in patients with end-stage renal disease and use of sacubitril valsartan is not recommended. It should be noted that like ACE inhibitors and ARB agents, prescription of sacubitril valsartan can be associated with decreased renal function.

Caution is needed when Sacubitril valsartan is used alongside other drugs which affect serum potassium levels.

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or angiotensin II receptor antagonists.

Interactions between sacubitril valsartan and lithium have not been investigated. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased further.

Initiation of therapy and ongoing dose regimen

Consultant Cardiologist initiation only

Initial dose and administration:
Treatment will be initiated by the specialist team (under the supervision of a Consultant Cardiologist). The specialist team will be responsible for prescribing until the patient is stabilised.

ACE Inhibitors must be stopped at least 36 hours prior to starting sacubitril/valsartan, due to the potential risk of angioedema when used concomitantly with an ACE inhibitor.

Patients established on full dose ACE inhibitor/ARB *and* SBP ≥110mmHg

- Starting dose 49mg/51mg twice daily for those on full dose ACE inhibitor or ARB (e.g. ramipril 10mg daily) and systolic blood pressure ≥110mmHg

Double the dose after 2 to 4 weeks to a maximum of 97mg/103mg twice daily if tolerated.

Patients on less than full dose ACE inhibitor/ARB or with SBP ≥100 to 110 mmHg

- Starting dose 24mg/26mg twice daily if on less than full dose ACE inhibitor/ARB or systolic blood pressure <110mmHg

Double the dose every 3 to 4 weeks to 49mg/51mg twice daily and then 97mg/103mg twice daily if tolerated.

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

If a dose is missed, the tablet should be taken at the next scheduled time.
Tablets should be swallowed whole with water and can be taken with or without food.

Maintenance dose and administration:
Once the patient is stabilized the GP should continue the currently prescribed dose.

Dose adjustments should only be made by, or after discussion with, the specialist team.

Duration of therapy / How the treatment will be reviewed and if appropriate, stopped

Lifelong unless discontinued due to lack of efficacy / futility or because of adverse events e.g. patient entering end of life care, development of end stage renal.

Baseline assessment and ongoing monitoring – by Specialist

Renal function Serum potassium Blood pressure

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.

Review of the patient's treatment in regular outpatient appointments (minimum six monthly). Changes to therapy as a result of these reviews (or at any other time) should be reported to the GP promptly

GP / Community Team or other Primary Care monitoring responsibilities

Monitor renal function and electrolytes every six months and more often during periods of illness referring to the specialist team where necessary.

Measure and record blood pressure and heart failure symptoms such as ankle swelling.

Consultant / Specialist prescribing responsibilities

- To initiate and stabilise treatment before transfer to GP prescribing under shared care arrangements
- To provide the GP with appropriate prescribing information and any additional information requested
- To be available for advice if the patient's condition changes
- To contact patient's GP to request prescribing under shared care and send a copy of the shared care protocol.
- To provide the GP with a summary of information relating to the individual patient to support the GP in undertaking shared care
- To advise the GP of any dosage adjustments required, monitoring required, when to refer back and when and how to stop treatment
- To ensure that procedures are in place for the rapid re-referral of the patient by the GP
- To monitor the patient and their therapy at six monthly intervals.
- To monitor the patient for adverse events and report to the GP and where appropriate Commission on Human Medicines/MHRA (Yellow card scheme).
- To provide the GP with contact details in case of queries.

GP prescribing responsibilities

- Initially refer the patient for specialist advice where not already under the care of a heart failure team

- To continue to prescribe sacubitril valsartan as part of a shared care arrangement, at least 4 weeks after treatment has been initiated
- To ensure there are no interactions with any other medications initiated in primary care.
- To monitor renal function and electrolytes every six months and more often during periods of illness referring to the specialist team where necessary. Consider referral where any significant decrease in renal function is noted
- To measure and record blood pressure and heart failure symptoms such as ankle swelling, referring to the specialist team where necessary
- To refer back to the specialist where appropriate. For example: Patient or general practitioner is not comfortable to continue with the existing regime due to either change in condition or drug side effects.
- To monitor concordance with therapy and raise concerns with the specialist team as appropriate.
- Discontinue the drug as directed by the specialist if required
- To identify adverse events if the patient presents with any signs and liaise with the hospital specialist where necessary.
- To report adverse events to the specialist and where appropriate the Commission on Human Medicines/MHRA (Yellow card scheme).

Indications for referral back to Specialist

Stop sacubitril valsartan treatment and refer to specialist if:

- Patient becomes pregnant
- Significant hypotension, hyperkalaemia or acute renal impairment occur

Continue treatment but refer to specialist if deterioration in the patient's heart failure symptoms

Author(s) and Organisation	• Dr Rajah Nata – Consultant Cardiologist, Queen Elizabeth Hospital King's Lynn • Mr David Homer - Associate Chief Pharmacist, Queen Elizabeth Hospital Kings Lynn • Dr Alisdair Ryding - Consultant Cardiologist, NNUH. • Dr Cairistine Grahame-Clarke - Consultant Cardiologist, NNUH. • Dr Sunil Nair - Consultant Cardiologist, NNUH • Updated to new template by JC, TAG Lead Technician, NWICB
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Version	Date	Author / Editor	Status	Comment
1.0	Sept 2016	Mr DH QEH & Dr AR NNUH FM, TAG Lead Pharmacist, NEL CSU Anglia	Draft	For consideration by the Therapeutics Advisory Group (TAG) September 2016 (versions from the QEH and NNUH combined for the TAG)
1.1	Sept 2016	As for 1.0 above	Draft	Supported by the Therapeutics Advisory Group (TAG) September 2016 subject to minor alterations
1.2	Sept 2016	As for 1.0 above	Final - Current	Version 1.1. considered by the N&W D&TCG. Minor alterations to the text on page 1. regarding general principles for shared care prescribing recommended regarding GPs letting specialists know if they are ***not*** going to participate.
2.0	Dec 2018 – January 2019	Mr DH QEH & Dr AR NNUH FM, TAG Lead Pharmacist, AGEM CSU	Draft - Final	Logos updated – checked against current SPC. For consultation with authors. Supported by the authors. Supported by the TAG – January 2019.
3.0	Aug 2021	JC, TAG Lead Technician, NWICB	FINAL	Discussed at August 2021 TAG meeting. Review dates extended for a year from meeting due to covid pressures
4.0	March 2024	JC, TAG Lead Technician, NWICB	Final	Existing SCA transferred to new template ready for publishing on KNoW. Content not reviewed