SHARED CARE GUIDELINE FOR THE USE OF SACUBITRIL VALSARTAN FOR TREATING SYMPTOMATIC CHRONIC HEART FAILURE WITH REDUCED EJECTION FRACTION

INDICATION

Sacubitril-valsartan (Entresto®) is an angiotensin receptor neprilysin inhibitor, including both a neprilysin inhibitor (sacubitril) and the angiotensin II receptor blocker (ARB) valsartan. It is licensed for use in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.

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.

Sacubitril-valsartan should not be co-administered with an ACE inhibitor or an ARB. Due to the potential risk of angioedema when used concomitantly with an ACE inhibitor, it must not be started for at least 36 hours after discontinuing ACE inhibitor therapy. The combination of sacubitril-valsartan with direct renin inhibitors such as aliskiren is not recommended.

Locally it is expected that initiation be done under the direct supervision of a consultant cardiologist. Once stabilised on treatment the responsibility for continued prescription of sacubitril valsartan would pass to the patient's GP.

AREAS OF RESPONSIBILITY FOR SHARED CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of sacubitril can be shared between the specialist setting and the patient's GP (if different). GPs are invited to participate. If the GP is not confident to undertake these roles, then he or she is 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.

Sharing of care assumes communication. The intention to share care is usually explained to the patient by the doctor initiating treatment. It is important that patients are consulted about treatment and are in agreement with it.

The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

REFERRAL AND INITIATION	
Specialist Responsibilities	
1	To assess the patient and establish the diagnosis, determine a management strategy and ensure appropriate follow-up in conjunction with the GP.
2	The specialist will: • initiate and stabilise treatment; • obtain consent from the patient's GP to continue prescribing once treatment has been stabilised (usually after a minimum of 4 weeks); • monitor the patient and their therapy at six monthly intervals.
3	To provide the GP with appropriate prescribing information and any additional information requested.
4	To be available for advice if the patient's condition changes.
5	To ensure that procedures are in place for the rapid re-referral of the patient by the GP.
6	To ensure the patient has given informed consent to their treatment.
7	To liaise with the GP on any suggested changes in prescribed therapy.

General Practitioner Responsibilities	
1	Initially refer the patient for specialist advice where not already under the care of a heart failure team
2	Where appropriate to continue to prescribe sacubitril valsartan as part of a shared care arrangement, usually at least 4 weeks after treatment has been initiated
3	Measure and record blood pressure and heart failure symptoms such as ankle swelling, referring to the specialist team where necessary (suggested threshold for referral SBP ≤95mmHg)
4	Monitor renal function and electrolytes at least annually 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. Discontinue if the patient's eGFR <30 mL/min/1.73m^2
5	Deal with general health issues of the patient
6	Monitor concordance with therapy and raise concerns with the specialist team as appropriate

Patient's role (or that of carer)	
1	Report to the specialist or GP if he or she does not have a clear understanding of the treatment
2	Attend appropriate GP and other follow up appointments
3	Share any concerns in relation to treatment with sacubitril valsartan
4	Use written and other information provided with the medication and by the healthcare team
5	Seek help urgently if suspecting side-effects, or otherwise unwell

SUPPORTING INFORMATION

Dosage and Administration

The recommended starting dose is either 100 mg (49mg/51mg) twice daily, or 50 mg (24mg/26mg) twice daily for people not currently taking (or on low doses of) an angiotensin-converting enzyme (ACE) inhibitor or an ARB. A starting dose of 24 mg/26 mg twice daily should be considered for

patients with SBP ≥100 to 110 mmHg. The dose should be doubled every 2 to 4 weeks to the target of 200 mg (97mg/103mg) twice daily, as tolerated by the patient.

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.

Due to the potential risk of angioedema when used concomitantly with an ACE inhibitor, it must not be started for at least 36 hours after discontinuing ACE inhibitor therapy

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.

Contraindications

- Treatment should not be initiated in patients with serum potassium level >5.4 mmol/l or with SBP <100 mmHg
- 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 m^2)
- 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) (see section 5.1) Entresto® 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 Entresto® 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 Entresto® 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 Entresto® 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.

Side effects

The most commonly reported adverse reactions during treatment with sacubitril valsartan were hypotension, hyperkalaemia and renal impairment, the risk of which is increased by dehydration or concomitant use of non-steroidal anti-inflammatory agents (NSAIDs).

Interactions
The following drugs are contraindicated with Entresto®:

- ACE inhibitor containing products
- Aliskiren
- ARB containing products

Caution is needed in patients taking statins as use of Entresto® may increase the systemic exposure 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.

Entresto® taken with sildenafil is associated with significantly greater blood pressure reduction compared to administration of Entresto® alone. Therefore, caution should be exercised when sildenafil or another PDE5 inhibitor is initiated in patients treated with Entresto®.
Co-administration of Entresto® 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 LBQ657 or valsartan.

Co-administration of Entresto® with metformin reduced both C_{max} and AUC of metformin by 23%. The clinical relevance of these findings is unknown. Therefore, when initiating therapy with Entresto® in patients receiving metformin, the clinical status of the patient should be evaluated.

This list is not exhaustive. The manufacturer's summary of product characteristics (SPC) and the most current edition of the British National Formulary should be consulted for full information on contra-indications, warnings, side-effects and drug interactions.

Drug costs (Drug Tariff December 2016):

50 mg (sacubitril 24mg/valsartan 26mg)	28 pack: £45.78
100 mg (49mg/51mg)	56 pack: £91.56
200 mg (97mg/103mg)	56 pack: £91.56

References

NICE TA guidance 'Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction' available at https://www.nice.org.uk/guidance/TA388 , accessed 02/12/16

Summary of product characteristics for Sacubitril valsartan (Entresto®®) tablets available at http://www.medicines.org.uk/emc/medicine/31244 , accessed 02/12/16

Developed by	Cardiology Working Group, April 2016
Approved by	Dorset Medicines Advisory Group May 2016
Safety update	Cardiology Working Group, October 2016
Review date	May 2018 or before if new evidence or recommendations.