Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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sacubitril/valsartan 24mg/26mg, 49mg/51mg and 97mg/103mg film-coated tablets (Entresto®)

SMC No. (1132/16)

Novartis Pharmaceuticals UK Ltd

05 February 2016

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

sacubitril/valsartan (Entresto®) is accepted for use within NHS Scotland.

Indication under review: in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.

Sacubitril/valsartan, compared to an angiotensin-converting enzyme inhibitor, significantly reduced rates of the composite outcome of cardiovascular death and hospitalisation for heart failure, rates of the component outcomes and of all cause mortality.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 07 March 2016

Indication

In adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.

Dosing Information

The recommended starting dose is one tablet of 49mg/51mg twice daily, except in the situations described below. The dose should be doubled at two to four weeks to the target dose of one tablet of 97mg/103mg twice daily, as tolerated by the patient. The summary of product characteristics provides details of patients for whom a lower starting dose of 24 mg/26 mg twice daily is recommended.

Sacubitril/valsartan may be administered with or without food and the tablets must be swallowed with a glass of water.

Product availability date

07 December 2015.

Sacubitril/valsartan received a positive scientific opinion under the Early Access to Medicines Scheme (EAMS) with the Medicines and Healthcare Products Regulatory Agency on 1 September 2015.

Summary of evidence on comparative efficacy

Entresto® contains two medicines, sacubitril and valsartan, as a sacubitril valsartan sodium salt complex. After oral administration, it dissociates into valsartan and the prodrug, sacubitril, which is further metabolised to the active metabolite LBQ657. Together, they act as an angiotensin receptor neprilysin inhibitor. LBQ657, a first in class neprilysin (neutral endopeptidase) inhibitor, acts to block the degradation of several vasoactive peptides (e.g. natriuretic peptides), thereby enhancing the protective neurohormonal systems of the heart peptides. Valsartan is an established angiotensin II receptor blocker (ARB). The valsartan contained within Entresto® is more bioavailable than the valsartan in other marketed formulations, and the 26mg, 51mg and 103mg doses of valsartan in Entresto® are equivalent to 40mg, 80mg and 160mg of valsartan, respectively, in other marketed formulations.[1]

The evidence to support the use of sacubitril/valsartan comes from one randomised, double-blind, phase III study (PARADIGM-HF) which compared the efficacy and safety of sacubitril/valsartan with enalapril in 8,399 patients with chronic heart failure (CHF) and reduced ejection fraction.[1,2,3,5] Eligible patients were aged ≥18 years and had CHF New York Heart Association (NYHA) class II to IV with reduced left ventricular ejection fraction (LVEF) ≤40% (later amended to ≤35%). They had plasma B-type natriuretic peptide (BNP) level ≥150 picograms/mL or N-terminal pro-BNP level (NT-proBNP) ≥600 picograms/mL (or BNP level ≥100 picograms/mL or NT-proBNP level ≥400 picograms/mL if hospitalised for heart failure within the previous 12 months). They had been receiving a stable dose of angiotensin converting enzyme (ACE) inhibitor or ARB (equivalent to enalapril 10mg daily) and a stable dose of a beta-blocker (unless contra-indicated or not tolerated) for ≥four weeks before screening. Although not required, if a patient was receiving an aldosterone antagonist, the dose should also have been stable for at least four weeks before screening. The study comprised three phases: a screening phase, a single-blind run-in of enalapril, followed by a single-blind run-in of sacubitril/valsartan and then a double-blind treatment phase where eligible patients were randomised to sacubitril/valsartan or enalapril.

Eligible patients were switched from their pre-screening ACE inhibitor or ARB to enalapril (10mg twice daily, or if taking a lower dose of ACE inhibitor or ARB, 5mg twice daily initially, which was then uptitrated to 10mg twice daily) for a single-blind, run-in period. Those with no unacceptable side effects were then treated with a second, single-blind, run-in of sacubitril/valsartan 100mg (49mg/51mg) twice daily, increased to 200mg (97mg/103mg) twice daily, over four to six weeks. Patients with no unacceptable side effects on the target doses of study medications during the run-ins were randomised equally to double-blind treatment with sacubitril/valsartan (200mg [97mg/103mg] twice daily, n=4,187) or enalapril (10mg twice daily, n=4,212). The dose of study medication could be reduced in patients with unacceptable side effects on the target dose. Patients remained on an optimal background heart failure treatment which included a stable dose of a beta-blocker with or without an aldosterone antagonist and, if possible, the doses remained stable during the study. Diuretics could be used and adjusted throughout the study at the discretion of the investigator.[2,3,5]

The primary outcome was a composite of cardiovascular death or first hospitalisation for heart failure. The study was event-driven and included three planned interim analyses, performed after one third, one half and two thirds of the required number of events (2,410) had occurred. If there was compelling benefit in both the primary outcome and cardiovascular death, the study could be stopped early. At the third interim analysis, after a median follow-up of 27 months, the pre-specified stopping boundary was crossed and the study was stopped early (cut-off date of 31 March 2014 for all efficacy analyses).[2,3,5]

The composite primary outcome had occurred in significantly fewer sacubitril/valsartan than enalapril patients (22% versus 27%). Details of this, its components and secondary outcomes are presented in Table 1 below. Results for pre-specified subgroup analyses showed a consistent treatment effect.

Table: primary and secondary outcomes of the PARADIGM-HF study[1,2,5]

Outcome	Sacubitril/valsartan	Enalapril	Hazard ratio*/difference (95% CI), p-value
Primary outcome and its components			
Cardiovascular death or hospitalisation due to heart failure % (n/N)	22% (914/4,187)	27% (1,117/4,212)	0.80 (0.73 to 0.87) p<0.001
Cardiovascular death % (n/N)	13% (558/4,187)	16% (693/4,212)	0.80 (0.71 to 0.89) p<0.001
Hospitalisation due to heart failure % (n/N)	13% (537/4,187)	16% (658/4,212)	0.79 (0.71 to 0.89) p<0.001
Secondary outcomes			
Death from any cause % (n/N)	17% (711/4,187)	20% (835/4,212)	0.84 (0.76 to 0.93) p<0.001
LS mean change in KCCQ clinical summary score from baseline to 8 months	-2.99	-4.63	1.64 (0.63 to 2.65) p=0.001
New onset atrial fibrillation % (n/N)	3.1% (84/2,670)	3.1% (83/2,638)	0.97 (0.72 to 1.31) p=0.83
Decline in renal function % (n/N)	2.2% (94/4,187)	2.6% (108/4,212)	0.86 (0.65 to 1.13) p=0.28

CI=confidence interval; LS = least squares; * hazard ratio derived from Cox proportional hazards model.
KCCQ: Kansas City Cardiomyopathy Questionnaire is a self-administered questionnaire which ranges from 0 to 100 with higher scores indicating fewer symptoms and physical limitations associated with heart failure.
New onset of atrial fibrillation was assessed in the patients without atrial fibrillation at baseline
Decline in renal function was defined as end stage renal disease (ESRD) or a decrease in estimated glomerular filtration rate (eGFR) from randomisation of >50% or of >30mL/min/1.73m^2 to a value <60mL/min/1.73m^2.
EuroQoL visual analogue scale (EQ-5D VAS) was also assessed as an exploratory outcome.[4]

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

During the single-blind, run-in phases of the study, 12% of patients discontinued due to an adverse event overall: 5.6% during the enalapril run-in period (due to renal dysfunction [1.7%], hyperkalaemia [1.7%] and hypotension [1.4%]) and 5.9% during the sacubitril/valsartan run-in period (due to renal dysfunction [1.8%], hypotension [1.7%] and hyperkalaemia [1.3%]).[1] The discontinuation rate was higher in the enalapril group than the sacubitril/valsartan group when adjusted for the shorter duration of run-in treatment (median 15 days and 29 days respectively).[2]

During the double-blind treatment phase, adverse events were reported by 81% (3,419/4,203) of sacubitril/valsartan patients and 83% (3,503/4,229) of enalapril patients, and these were considered treatment-related in 22% (910/4,203) and 23% (976/4,229) of patients respectively. Serious adverse events were reported by 46% (1,937/4,203) of sacubitril/valsartan patients and 51% (2,142/4,229) of enalapril patients. Adverse events led to discontinuations in 11% (450/4,203) of sacubitril/valsartan patients and 12% (516/4,229) of enalapril patients during the double-blind phase (p=0.03). [2,4,5]

The most frequently reported adverse events in the sacubitril/valsartan and enalapril groups respectively were: hypotension (18% and 12%), cardiac failure (17% and 20%), hyperkalaemia (12% and 14%), renal impairment (10% and 12%), cough (8.8% and 13%), dizziness (6.3% and 4.9%), atrial fibrillation (6.0% and 5.6%), pneumonia (5.4% and 5.6%) and dyspnoea (5.1% and 7.2%).[2]

Symptomatic hypotension was significantly more common in the sacubitril/valsartan group than in the enalapril group (14% versus 9.2% respectively, $p<0.001$). The incidence of cough (11% versus 14%), serum creatinine ≥2.5mg/dL (3.3% versus 4.5%) and serum potassium >6.0mmol/L (4.3% versus 5.6%) were significantly lower in the sacubitril/valsartan group than in the enalapril group ($p<0.05$).[2]

The most frequently reported serious adverse events in the sacubitril/valsartan and enalapril groups respectively were: cardiac failure (14% and 15%), pneumonia (3.7% and 4.3%), chronic cardiac failure (2.7% and 3.2%), congestive cardiac failure (2.7% and 3.3%), atrial fibrillation (2.6% and 2.7%) and cardiac death (2.0% and 2.7%).[2]

The incidence of angioedema was adjudicated by a blinded expert committee. There was a total of 19 confirmed cases in the sacubitril/valsartan group and 10 in the enalapril group. The airway was not compromised in any patient and no patients required intubation.[2]

*Other data were also assessed but remain commercially confidential.**

Summary of clinical effectiveness issues

Sacubitril/valsartan represents a new therapeutic option for patients with chronic heart failure and reduced ejection fraction and would be used instead of an ACE inhibitor or ARB. Sacubitril is the prodrug of LBQ657, a first in class neprilysin inhibitor, which enhances the protective neurohormonal systems of the heart peptides (eg natriuretic peptides). Valsartan is an established ARB.[1] Clinical experts consulted by SMC considered that there is an unmet need for more effective treatments in the management of heart failure.

The composite primary outcome of the pivotal PARADIGM-HF study included two direct health outcomes (cardiovascular death and hospitalisation due to heart failure) and there was a significant reduction with sacubitril/valsartan versus enalapril (absolute reduction of 4.7%, relative risk reduction of 20%, number needed to treat [NNT] over 27 months of 21). The reduction was significant and

consistent in each of the components and considered clinically relevant: cardiovascular death (absolute reduction of 3.1%, relative risk reduction of 20%, NNT of 32) and hospitalisation due to heart failure (absolute reduction of 2.8%, relative risk reduction of 21%, NNT of 36).[1,2]

The study compared sacubitril/valsartan, which included a valsartan dose equivalent to 160mg twice daily, with enalapril 10mg twice daily. Although doses of both medicines are within the target doses recommended by guidelines (valsartan 160mg twice daily and enalapril 10 to 20mg twice daily), the enalapril dose is at the lower end of the recommended target dose. However this is similar to the enalapril dose used in other heart failure studies and used in clinical practice.[5,7,8]

The PARADIGM-HF study patients had symptomatic heart failure, with mainly mild to moderate severity of symptoms and limitation of physical activity (70% of patients had NYHA class II, and 24% had class III). There were limited numbers of patients with NYHA class IV disease (n=60). They had received previous treatment with stable doses of ACE inhibitor (78%) or ARB (23%) for at least four weeks before screening.[2] The study did not include treatment-naive patients or patients with worsening symptoms of heart failure who may be more likely to be considered for new medicines in clinical practice as part of initiation or a change in therapy. However, despite the study including stable patients, an additional treatment effect was still demonstrated with sacubitril/valsartan over enalapril. The treatment effect in new or deteriorating patients remains unclear. Although sacubitril/valsartan had a greater effect on blood pressure than enalapril, analyses indicated that the treatment benefit seen in PARADIGM-HF was likely to be independent of this.[2]

The study included run-in phases to ensure that randomised patients could tolerate the target doses of both study medicines and to minimise large drop-out rates. However, as a result, the incidence of adverse events during the double-blind phase of the study may underestimate the incidence expected in clinical practice without a run-in period. In addition, the sequence of run-ins, with enalapril performed first, may have limited the available data on sacubitril/valsartan.[1,5]

Study patients were required to have elevated plasma BNP or NT-proBNP levels at baseline.[2] Since this does not appear to be routinely measured currently, it may be difficult to identify patients in clinical practice who reflect the study population. Study patients were generally of younger age (mean of 64 years) than expected in practice (mean of 76 years at first diagnosis).[6] The study also excluded patients with SBP<100mmHg, severe renal impairment and severe hepatic impairment.[2]

The summary of product characteristics recommends slower initial dose titration of sacubitril/valsartan for patients on no or low doses of ACE inhibitor or ARBs.[1] Results from a randomised, double-blind, phase II, 12-week study (TITRATION) in 498 patients with CHF (NYHA class II to IV) and reduced ejection fraction (LVEF ≤35%), showed that more patients in a low Renin-Angiotensin-Aldosterone System subgroup (i.e. patients naive to ACE inhibitors or ARBs or on low-dose) achieved and maintained the target dose of sacubitril/valsartan when the dose was up-titrated over six weeks than over three weeks.[1,9,10]

There are no direct comparative data with ACE inhibitors, other than enalapril, or with any ARB. The company presented results of a Bayesian network meta-analysis (NMA) to allow indirect comparison of sacubitril/valsartan with ARB in patients with heart failure, NYHA class II to IV, and reduced LVEF. Three outcomes were evaluated: all cause mortality, cardiovascular mortality and all cause hospitalisation. The results were used to support the secondary comparison in the economic case for patients who cannot tolerate the first-line use of ACE inhibitors. The core NMA included a total of 28 studies and did not consider concomitant treatment. Comparators were considered as therapeutic classes (ARB and ACE inhibitors) as opposed to individual medicines and assumed equal efficacy of all medicines within the class. The NMA hazard ratio point estimate results indicate that sacubitril/valsartan is more effective than ARBs in terms of all cause mortality and cardiovascular mortality. However, the credible intervals were wide and included 1, indicating no real difference due

to uncertainty from heterogeneity among the studies. All cause hospitalisation appeared similar with sacubitril/valsartan and ARBs. Meta-regression for treatment effect modifiers and scenario analyses, categorising treatments based on consideration of concomitant treatment, with beta-blockers and/or aldosterone agonists, did not impact these results. The validity of the results is limited by heterogeneity among studies, particularly in the durations of studies and the outcomes assessed. However, there is reassurance in that the results of the NMA, between sacubitril/valsartan and ACE inhibitors, were similar to results from direct evidence of the PARADIGM-HF study, and between ACE inhibitors and ARBs, were similar results to results of a Cochrane review.[11] The wider credible intervals computed in the NMA again indicate uncertainty resulting from heterogeneity in the indirect evidence.

The introduction of sacubitril/valsartan would offer an alternative treatment to ACE inhibitors or ARBs in patients with heart failure and reduced ejection fraction. This was associated with an additional reduction in the risk of cardiovascular death and hospitalisation due to heart failure over the reduction seen with enalapril. However, due to the early stopping of the study, it is unclear if the mortality benefit is sustained over time and if there are any longer term adverse events associated with neprilysin inhibition.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing sacubitril/valsartan plus standard care with enalapril plus standard care in patients with symptomatic chronic heart failure with reduced ejection fraction. Enalapril was assumed to be representative of all ACE inhibitors. Standard care included a range of background therapies used to treat common comorbidities associated with heart failure, as well as a range of treatments used for the prevention of cardiovascular disease. A secondary comparison was provided with ARBs. SMC clinical experts confirmed the comparators included in the analysis are appropriate, with ACE inhibitors the treatment most likely to be displaced in practice.

A Markov model was used which consisted of two health states, alive and dead, where the alive health state included the rates of hospitalisations, adverse events, and changes in quality of life over time. The model used the baseline characteristics and associated risks of each patient from the PARADIGM-HF study to produce individual results for each patient. The outcomes for each patient were then averaged to give the results for the whole study population. A lifetime horizon (30 years) was used and was justified on the basis that heart failure is a chronic condition which requires lifelong treatment. Shorter time horizons between 1 and 30 years were explored in the sensitivity analysis.

The main source of clinical data was the PARADIGM-HF study where survival and hospitalisation rates were measured. In the economic model, the primary outcome of cardiovascular mortality was not used in the base case analysis, but instead survival was modelled using the secondary outcome of all-cause mortality. An alternative survival modelling approach was provided in the sensitivity analysis where cardiovascular mortality was modelled using the primary outcome measure, but the results were not sensitive to using this alternative approach. Similarly, the outcome of all-cause hospitalisation was used in the model instead of hospitalisation due to heart failure. For the comparison with ARBs, clinical data used in the model were taken from the NMA.

Survival was extended beyond the clinical study follow-up period using parametric survival analysis. The company selected the Gompertz function to extrapolate the all-cause mortality data in the model based on expert opinion. The Weibull function was the best fit to the data based on goodness of fit statistics, but the differences between the best fitting functions were small. The company noted that the Gompertz function resulted in the shortest survival and can therefore be considered conservative in terms of estimating the survival benefit of sacubitril/valsartan. The treatment effects of

sacubitril/valsartan, both in terms of survival and hospitalisations, were assumed to continue for the duration of the model.

The utility values were taken from EQ-5D data collected in the PARADIGM-HF study. As the model used patient-level data, the utility values were specific to each patient modelled. The company noted the mean utility value at baseline was 0.78 and an annual decline in quality of life of 0.008 was applied in both arms. After controlling for the effects of hospitalisation and adverse events, sacubitril/valsartan was associated with a small (0.011) but statistically significant additional effect on quality of life. A disutility of 0.105 was applied for the first 30 days post hospitalisation and a disutility of 0.054 for days 30 to 90. Disutilties were also included for the adverse events of cough and hypotension.

The analysis included the medicine acquisition costs of sacubitril/valsartan and enalapril, plus the standard care and background medication costs patients received in the PARADIGM-HF study. Costs associated with adverse events were included in the model based on the adverse events observed in the PARADIGM-HF study, with the resource use requirements for treating adverse events derived from a company advisory board. The adverse events included were hypotension, cough, elevated serum creatinine, elevated serum potassium, and angioedema. Hospitalisation costs were included using the hospitalisation rates from the PARADIGM-HF study, with separate costs included for cardiovascular and non-cardiovascular hospitalisations. Background resource use was applied equally in both arms based on data from a published UK study and included A&E, outpatient, and GP visits.

For the comparison with enalapril, the company estimated a base case cost per QALY of £18,348 based on an incremental cost of £7,685 and a QALY gain of 0.42. A secondary comparison was provided with ARBs which resulted in a cost per QALY of £16,621 based on an incremental cost of £9,434 and a QALY gain of 0.57. A range of sensitivity and scenario analyses was provided which showed the results were most sensitive to the survival estimates, the duration of the treatment effect, and the time horizon. The results were not overly sensitive to the inclusion of the additional quality of life benefit in the sacubitril/valsartan arm, as when this was removed, the incremental cost-effectiveness ratio (ICER) only increased to £22k per QALY.

The following limitations were noted:

- There was some uncertainty about the magnitude of the clinical benefit with sacubitril/valsartan given the concerns about the generalisability of the clinical evidence to Scottish practice. In particular, the dose of enalapril used in the pivotal study is at the lower end of the target dose. In order to explore this uncertainty, the company provided additional sensitivity analyses to show the impact of assuming a smaller mortality benefit with sacubitril/valsartan. When the mortality benefit was reduced by 10%, 20% and 30%, the ICER increased to £20k, £21k, and £24k respectively. Additional responses received from SMC clinical experts indicated the dose of enalapril used in the study is consistent with clinical practice.
- The treatment effect of sacubitril/valsartan was assumed to continue throughout the model time horizon with no reduction in the treatment effect over time. Sensitivity analysis showed the results were sensitive to this assumption, with the ICER increasing to £32k for the comparison with enalapril when the treatment effect was assumed to cease at 5 years.
- The model used the secondary endpoint of all-cause mortality to estimate survival and sensitivity analysis showed the results were sensitive to the survival estimates. Using the lower 95% confidence interval increased the cost per QALY to £34k. However, the company also provided an analysis which used the primary endpoint of cardiovascular mortality and then applied non-cardiovascular mortality using Scottish life tables. This resulted in a small reduction in the ICER to £17k.
- The run-in phases of the study may result in lower adverse event and discontinuation rates than would be expected in clinical practice. Although these are unlikely to be key drivers in the model, the company provided additional sensitivity analysis in order to capture this uncertainty.

Assuming a five-fold increase in the adverse event rate and a three-fold increase in the discontinuation rate increased the ICER to £21k.

- In order to address the combined uncertainty of a number of parameters in the model, the company provided a conservative scenario analysis which reduced the mortality benefit by 10%, assumed no treatment effect beyond 10 years, removed the additional quality of life benefit, and reduced the baseline utility value to 0.72. In this scenario, the ICER increased to £28k.
- For the secondary comparison with ARBs, the NMA indicates that the treatment benefit of sacubitril/valsartan over ARBs is uncertain. The differences between the treatments in terms of all-cause mortality, cardiovascular mortality, and all-cause hospitalisation were not statistically significant but the numerical differences were included in the model. Additional sensitivity analysis was provided which showed that when the benefit of sacubitril/valsartan on reducing all-cause hospitalisation was removed, the hazard ratio for all-cause mortality could increase to 0.936 (from a base case value of 0.81) before the ICER increased to £30k.

Despite the limitations outlined above, the economic case has been demonstrated.

Summary of patient and public involvement

The following information reflects the views of the specified Patient Group.

- A submission was received from Chest, Heart & Stroke Scotland, which is a registered charity.
- Chest, Heart & Stroke Scotland has not received any pharmaceutical company funding in the past two years.
- People with heart failure describe a range of symptoms which impact on their quality of life. Shortness of breath both at rest and during exertion leads to many socially withdrawing leading to a loss of friends and a sense of purpose in life. The most common issue raised is the restrictions their condition places on things that are important to the person - such as hobbies/going out/gardening etc and the fear of being a burden to others.
- Patients felt that they were well cared for but welcomed the new treatment if it might reduce their risk of dying as it would make them feel less worried and more positive about their future. Some people were concerned about having to come off a tablet that they had been on for years (to move to a new one).
- Patients' families particularly welcomed the possibility of a new treatment that could reduce the risk of early death. Patients' biggest concern is to have a treatment that improves their quality of life by improving symptoms such as breathlessness. People feel that they would need much more easy to understand information before they made a personal choice to change their treatment.

Additional information: guidelines and protocols

The European Society of Cardiology (ESC) published "Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012".[7] This guideline recommends the following in potentially all patients with systolic heart failure to reduce the risk of heart failure hospitalisation and the risk of premature death:

• an ACE inhibitor (or if not tolerated, an ARB) in addition to a beta-blocker, for all patients with symptomatic heart failure (NYHA II to IV) and an ejection fraction ≤40%.
• a mineralocorticoid receptor antagonist (spironolactone or eplerenone) for all patients with persisting symptoms (NYHA II to IV) and an ejection fraction ≤35%, despite treatment with an ACE inhibitor (or ARB if ACE inhibitor not tolerated) and a beta-blocker.

The guideline also notes a number of other treatments with less certain benefits which should be considered in patients with symptomatic NYHA II to IV systolic heart failure, including ivabradine, digoxin, hydralazine and isosorbide dinitrate.

The National Institute for Health and Clinical Excellence (NICE) published clinical guideline 108 "Chronic Heart Failure" in August 2010.[6] This guideline recommends that both ACE inhibitors and beta-blockers licensed for heart failure should be offered to all patients with heart failure due to left ventricular systolic dysfunction. Specialist advice should be sought before offering second-line treatment to patients with heart failure due to left ventricular systolic dysfunction. Consider adding one of the following if a patient remains symptomatic despite optimal therapy with an ACE inhibitor and a beta-blocker:
• an aldosterone antagonist licensed for heart failure (especially if the patient has moderate to severe heart failure [NYHA class III to IV] or has had a myocardial infarction [MI] within the past month) or
• an ARB licensed for heart failure (especially if the patient has mild to moderate heart failure [NYHA class II to III]) or
• hydralazine in combination with nitrate (especially if the patient is of African or Caribbean origin and has moderate to severe heart failure [NYHA class III to IV]).

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline number 95 "Management of Chronic Heart Failure" in February 2007.[8] This guideline recommends that ACE inhibitors should be considered in patients with all NYHA functional classes of heart failure due to left ventricular systolic dysfunction and that beta-blocker therapy should be started as soon as their condition is stable (unless contraindicated by a history of asthma, heart block or symptomatic hypotension). Patients with chronic heart failure due to left ventricular systolic dysfunction alone, or heart failure, left ventricular systolic dysfunction or both following myocardial infarction (MI) who are intolerant of ACE inhibitors should be considered for an ARB. Patients with heart failure due to left ventricular systolic dysfunction who are still symptomatic despite therapy with an ACE inhibitor and a beta-blocker may benefit from the addition of candesartan, following specialist advice. Also, following specialist advice, patients with moderate to severe heart failure due to left ventricular systolic dysfunction should be considered for spironolactone unless contraindicated by the presence of renal impairment or a high potassium concentration. In patients who develop gynaecomastia, eplerenone can be substituted for spironolactone. Patients who have suffered a MI and with left ventricular ejection fraction ≤40% and either diabetes or clinical signs of heart failure should be considered for eplerenone unless contraindicated by the presence of renal impairment or a high potassium concentration. The SIGN website indicates that a review of this guideline is being considered.

Additional information: comparators

ACE inhibitors and ARBs. ACE inhibitors licensed in the UK for treatment of heart failure include captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril and ramipril. ARBs licensed in the UK for treatment of heart failure include candesartan, losartan and valsartan. A number of ACE inhibitors and ARBs, commonly prescribed for heart failure, are included in the cost table below.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Sacubitril/valsartan	**97mg/103mg twice daily**	**1,190**
Valsartan	160mg twice daily	58
Ramipril	5mg twice daily	32 to 36
Candesartan	32mg daily	29
Enalapril	10mg to 20mg twice daily	22 to 27
Lisinopril	35mg daily	41

Doses are for general comparison and do not imply therapeutic equivalence. These doses are the recommended target doses but may not be tolerated in all patients. Costs from eVadis on 17 November 2015 except for sacubitril/valsartan which is from the company submission.

Additional information: budget impact

The submitting company estimated there would be 30,567 patients eligible for treatment in year 1, rising to 31,066 in year 5. The uptake rate was estimated to be 2% (637 patients) in year 1, rising to 38% (11,858 patients) in year 5.

The company estimated a gross medicines budget impact of £761k in year 1, rising to £14.2m in year 5. As other medicines were assumed to be displaced, the net impact on the medicines budget was estimated to be £721k in year 1, rising to £13.4m in year 5.

SMC clinical expert responses indicate that the uptake rate in year 1 may be significantly higher than estimated by the submitting company.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Novartis Pharmaceuticals UK Ltd. Summary of product characteristics, Entresto®, 1 December 2015.

2. McMurray JJV, Packer M, Desai AS et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993-1004.

3. McMurray JJV, Packer M, Desai AS et al. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prosepctive comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). Europ J Heart Failure 2013;15:1062-73.

4. *Commercial in Confidence**

5. European Medicines Agency. CHMP assessment report for sacubitril/valsartan (Entresto®). EMA/671279/2015 24 September 2015.

6. National Institute for Health and Clinical Excellence (NICE). Clinical Guideline (CG) 108: Chronic Heart Failure, August 2010

7. European Society of Cardiology. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. European Heart Journal 2012; doi:10.1093/eurheartj/ehs104

8. The Scottish Intercollegiate Guidelines Network (SIGN). Guideline number 95: Management of Chronic Heart Failure, February 2007.

9. Senni M, Gogia H, Martinez M et al. Effect of baseline ACEI/ARB use on the safety and tolerability of uptitrating LCZ696 over 3 vs. 6 weeks: results from the TITRATION study [Abstract]. European Society of Cardiology: 2nd World Congress on Acute Heart Failure 2015.

10. Senni M, Reyes A, Majercak I et al. Results of the TITRATION study: a 12-week, multicentre, randomised, double-blind, safety evaluation of a 3- versus 6-week up-titration regimen of LCZ696 in patients with HFrEF [Poster]. European Society of Cardiology: 2nd World Congress on Acute Heart Failure 2015; P1795.

11. Heran BS, Musini VM, Bassett K et al. Angiotensin receptor blockers for heart failure. In: The Cochrane Collaboration, editor. Cochrane Database of Systematic Reviews 2012, Issue 4. Art. No.: CD003040. DOI: 10.1002/14651858.CD003040.pub2

This assessment is based on data submitted by the applicant company up to and including 08 January, 2016.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator

products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.