NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using sacubitril valsartan in the NHS in England. The Appraisal Committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, and clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 8) and the public. This document should be read along with the evidence base (the Committee papers).

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using sacubitril valsartan in the NHS in England.

For further details, see the Guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 15 January 2016

Second Appraisal Committee meeting: 10 February 2016

Details of membership of the Appraisal Committee are given in section 7, and a list of the sources of evidence used in the preparation of this document is given in section 9.

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

1 Appraisal Committee's preliminary recommendations

1.1 Sacubitril valsartan is recommended as an option for treating people with heart failure with reduced ejection fraction, only in people:

- with New York Heart Association (NYHA) class II to III chronic heart failure and
- who are already taking a stable dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor-blockers (ARBs) and
- with a left ventricular ejection fraction of 35% or less.

1.2 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 done by the heart failure specialist, or in primary care by either a GP with a special interest in heart failure or a heart failure specialist nurse.

1.3 People whose treatment with sacubitril valsartan is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2 The technology

2.1 Sacubitril valsartan (Entresto; Novartis) has a UK marketing authorisation for 'the treatment of symptomatic chronic heart failure with reduced ejection fraction'. Sacubitril valsartan is an angiotensin receptor neprilysin inhibitor, including both a neprilysin inhibitor (sacubitril) and an angiotensin II receptor blocker (ARB; valsartan). Both sacubitril and valsartan lower blood pressure.

2.2 Sacubitril valsartan is administered orally. The recommended starting dose is either 100 mg twice daily, or 50 mg twice daily for people not currently taking (or on low doses of) an angiotensin converting enzyme (ACE) inhibitor or an ARB. The dose should be doubled every 2 to 4 weeks to the target of 200 mg twice daily, as tolerated by the patient.

2.3 The most commonly reported adverse reactions during treatment with sacubitril valsartan were hypotension, hyperkalaemia and renal impairment. Reported adverse events were generally in line with that reported for other medicinal products acting on the renin-angiotensin-aldosterone system. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.4 The acquisition cost of sacubitril valsartan is as follows (excluding VAT; price confirmed by company):

- 50 mg, 28 pack: £45.78
- 100 mg, 28 pack: £45.78
- 100 mg, 56 pack: £91.56
- 200 mg, 56 pack: £91.56

Costs may vary in different settings because of negotiated procurement discounts.

3 The company's submission

The Appraisal Committee (section 9) considered evidence submitted by Novartis and a review of this submission by the Evidence Review Group (ERG; section 10).

Clinical effectiveness evidence

3.1 The pivotal clinical evidence presented in the company's submission was obtained from the PARADIGM-HF trial comparing sacubitril valsartan with enalapril (an angiotensin-converting enzyme [ACE] inhibitor). It also carried out a network meta-analysis to compare sacubitril valsartan with angiotensin II receptor-blockers (ARBs) for people who cannot have an ACE inhibitor. Finally, the company provided supplementary evidence in its submission from the TITRATION trial which evaluated the safety and tolerability of sacubitril valsartan at increasing doses.

3.2 PARADIGM-HF was a randomised, double-blind, controlled, phase III trial comparing sacubitril valsartan (n=4187) with enalapril (n=4212). Both treatments were given in combination with standard care (including beta blockers and aldosterone antagonists). The trial included people with symptomatic heart failure – that is, New York Heart Association (NYHA) class II to IV – with reduced left ventricular ejection fraction (LVEF) of 35% or lower. Enalapril was chosen as a comparator in the trial by the company because it is the ACE inhibitor that has been studied in the largest number of trials in this population.

3.3 The trial comprised 4 stages:

- Screening: for inclusion and exclusion criteria. Eligible patients were on a stable dose of an ACE inhibitor or an ARB equivalent

to enalapril 10 mg per day for 4 weeks or more before screening visit.

- Enalapril run-in (2 weeks): eligible patients were switched from current medication (ACE inhibitor or ARB) to single-blind treatment with enalapril (10 mg twice daily).
- Sacubitril valsartan run-in (4 to 6 weeks): patients were eligible if they had no unacceptable side effects in the previous stage. Eligible patients were switched to single-blind treatment with sacubitril valsartan at a dose of 100 mg twice daily, which was increased to 200 mg twice daily during the run-in stage. The 2 run-in stages were sequential, with only a brief (approximately 36 hours) washout period, and both included all eligible patients.
- Main trial: patients with no unacceptable side effects after taking target doses of the 2 study medications were randomly assigned (1:1) to double-blinded treatment with either sacubitril valsartan (200 mg twice daily) or enalapril (10 mg twice daily).

3.4 Although the inclusion criteria specified people with NYHA class II to IV, some people had an improvement in their NYHA class between screening and randomisation, so nearly 5% of randomised patients were NYHA class I. The LVEF entry criterion was initially 40% or lower but was subsequently reduced to 35% or lower (961 patients were randomised who had LVEF greater than 35%) in order to ensure an adequate event rate in the study population. Hospitalisation for heart failure within the last 12 months was also a necessary inclusion criterion.

3.5 The company stated that at baseline, most characteristics were balanced between the treatment groups, including age, geographic region, NYHA class, standard care or background therapies received, and medical histories. It also commented that patients in the trial were younger (only 49% were 65 years or older) and more

likely to be men (just 22% were women) than the general population seen in clinical practice in England. The company reported standard care and background therapies to be comparable to those in clinical practice in England; in the trial, at baseline, 93% of patients had beta blockers and 56% had aldosterone antagonists. About 78% had previously had an ACE inhibitor, and 23% had previously had an ARB. About 30% of people in the trial had been diagnosed with heart failure within the last year, 38% between 1 and 5 years previously, and 32% greater than 5 years previously.

3.6 Results were presented based on the full analysis set, which consisted of all patients except those who did not meet the eligibility criteria or did not have a single dose of the study drug. These data were used for the efficacy outcomes (n=8399). The primary end point was a composite of death from cardiovascular causes or a first hospitalisation for worsening heart failure, assessed at every study visit (0, 2, 4 and 8 weeks, 4 months, and then every 4 months). The composite primary end point significantly favoured sacubitril valsartan compared with enalapril (hazard ratio [HR] 0.80; 95% confidence interval [CI] 0.73 to 0.87, $p<0.001$).

3.7 The secondary outcomes included:

- all-cause mortality (assessed at all study visits)
- change from baseline to 8 months in the clinical summary score on the Kansas City Cardiomyopathy Questionnaire (KCCQ); patient scores were assessed at baseline/randomisation visit (visit 5), at 4, 8 and 12 months (visits 8, 9 and 10), at 24 and 36 months (visits 14 and 17), and at the end of study visit.

Sacubitril valsartan showed a significantly reduced risk compared with enalapril of all-cause mortality (HR 0.84; 95% CI 0.76 to 0.93, p<0.001), first all cause hospitalisation (HR 0.88; 95% CI 0.82 to 0.94, p<0.0001), and first cardiovascular hospitalisation (HR 0.88; 95% CI 0.81- 0.95, P<0.0008). The KCCQ patient scores were reduced for both sacubitril valsartan and enalapril; however, this reduction was less with sacubitril valsartan (by 2.99 points) than with enalapril (by 4.63 points).

3.8 Patients were stratified at randomisation by about 20 factors, which included region, NYHA class, systolic blood pressure, LVEF, prior ACE inhibitors, prior ARBs, prior aldosterone antagonists, and prior hospitalisation for heart failure. Sacubitril valsartan treatment reduced the risk of the primary composite end point when compared with enalapril, independent of all predefined subgroups, although not all were statistically significant.

3.9 The company stated that age, gender, and NYHA class were important factors because the baseline characteristics of patients in the trial were different from those seen in clinical practice in England. The primary composite outcome was statistically significant in favour of sacubitril valsartan compared with enalapril across all subgroups, except for in people aged 75 years and older (HR 0.86, 95% CI 0.72 to 1.04), and people with NYHA class III or IV heart failure (HR 0.92, 95% CI 0.79 to 1.08).

3.10 For the subgroups based on region, the primary composite outcome was statistically significant in favour of sacubitril valsartan compared with enalapril across all regions, except for the Western European subgroup (HR 0.89, 95% CI 0.74 to 1.07) and the Asia/Pacific and Other subgroup (HR 0.85, 95% CI 0.69 to 1.04). In the subgroup of patients who had not previously had an ACE inhibitor (n=1867), sacubitril valsartan showed an improvement in

the primary composite outcome of death from cardiovascular causes or a first hospitalisation for worsening heart failure, but this was not statistically significant (HR 0.92, 95% CI 0.76 to 1.10).

3.11 The NICE scope specified the comparator for people who cannot have an ACE inhibitor to be an ARB in combination with standard care. Because there is no head-to-head evidence comparing sacubitril valsartan with ARBs, the company conducted a network meta-analysis to inform the economic model with estimates of the effectiveness of sacubitril valsartan compared with ARBs, as well as the effectiveness of ARBs compared with ACE inhibitors.

3.12 The network meta-analysis was based on data from 28 randomised controlled trials and provided comparative evidence for all-cause mortality (28 trials, 4 treatment comparisons), cardiovascular mortality (13 trials, 4 treatment comparisons) and all-cause hospitalisations (28 trials, 4 treatment comparisons). The company commented that the network meta-analysis reflected the approach taken by the Cochrane meta-analysis, which assessed ACE inhibitors against ARBs with regard to morbidity and mortality irrespective of concomitant treatment with standard care therapies.

3.13 The network meta-analysis categorised treatment by class (angiotensin receptor neprilysin inhibitor [ARNI; sacubitril valsartan], ACE inhibitors, ARBs and placebo), assuming equal efficacy across all treatments in each class. To validate the class-effect assumption of ACE inhibitors, the company referenced a systematic review and network meta-analysis by Chatterjee et al. (2013) which found that 'there is currently no statistical evidence in support of the superiority of any single agent over the others'. The company referenced a Cochrane systematic review by Heran et al. (2012) to validate the assumption of a class effect for ARBs.

3.14 The company used a Bayesian framework for its network meta-analysis. The Bayesian network meta-analysis random effects model outcomes included all-cause mortality, cardiovascular mortality and all-cause hospitalisations. The results of the network meta-analysis presented by the company were designated academic in confidence and cannot be reported here. However, the results demonstrated that:

- ARBs and ACE inhibitors were broadly equivalent
- sacubitril valsartan was superior to ARBs with regards to all-cause and cardiovascular mortality and broadly equivalent with regards to all-cause hospitalisation outcomes
- sacubitril valsartan was superior to ACE inhibitors with regards to all-cause and cardiovascular mortality and superior with regards to all-cause hospitalisation.

3.15 The overall safety profile of sacubitril valsartan was comparable to that of the ACE inhibitor, enalapril, during the double-blind trial period of PARADIGM-HF. Compared with the enalapril group, fewer patients in the sacubitril valsartan group experienced 1 or more treatment-related adverse events, 1 or more serious adverse events, death or discontinued as a result of an adverse event. Treatment with sacubitril valsartan was associated with higher rates of hypotension. The company noted this was a result of sacubitril valsartan's greater vasodilator effect, and that there was no increase in the rate of discontinuation because of possible hypotension-related adverse effects. Fewer patients having sacubitril valsartan experienced renal adverse events compared with those having enalapril, which was driven by a lower incidence of renal impairment and renal failure in the sacubitril valsartan group (10.14% and 2.66% respectively) compared with the enalapril group (11.52% and 3.41% respectively). Other adverse

events that were more frequent in the enalapril group than in the sacubitril valsartan group were hyperkalaemia, cardiac failure, cough, dyspnoea, hypertension, hyperuricemia and constipation.

Cost-effectiveness evidence

3.16 The company submitted a 2-state Markov economic model with health states defined as 'alive' and 'dead'. In the base case, the model included all-cause mortality, all-cause-hospitalisation rates, EQ-5D and adverse event rates. The company stated that models with similar structures have been published previously, including the model submitted to NICE as part of its technology appraisal guidance on ivabradine for treating chronic heart failure. In its primary base-case analysis, patients entered in the model in either the sacubitril valsartan or the enalapril treatment arms to reflect the company's anticipated first-line positioning of sacubitril valsartan in the heart failure treatment pathway. The company also developed a secondary base-case model that included patients who cannot have ACE inhibitors; patients entered this model in either the sacubitril valsartan or ARB treatment arms. The ARB considered in the economic analysis was candesartan, and a class effect for ARBs was assumed.

3.17 The company's base-case analysis used individual patient-level data from the PARADIGM-HF trial, such that the model was run the same number of times as the number of patients included in the analysis (8399). Actual model outcomes were obtained by averaging across the 8399 individual patients' outcomes. The model used a cycle length of 1 month, and a half-cycle correction was applied to all calculations. The model was conducted over a lifetime horizon (equivalent to 30 years). Both costs and benefits were discounted at a rate of 3.5% and the perspective adopted was that of the NHS and personal social services. Deterministic and

probabilistic sensitivity analyses were also done to explore parameter uncertainty in the model.

3.18 The model population characteristics were based on the full analysis set population of PARADIGM-HF (see section 3.6). Baseline characteristics were used as covariates in the regression models to estimate mortality, hospitalisation and quality of life in the economic analysis.

3.19 In both treatment and comparator arms of the model, a proportion of patients had standard care (and other background therapies) in addition to sacubitril valsartan or enalapril (or candesartan). Standard care was defined as beta blockers and aldosterone antagonists. Additional background therapies consisted of diuretics, digoxin, anticoagulants, aspirin, adenosine diphosphate antagonists and lipid-lowering drugs.

3.20 The company's primary base-case analysis for sacubitril valsartan compared with enalapril modelled the likelihood of a patient experiencing a hospitalisation event using a negative binomial regression model. Predicted all-cause hospitalisation rates were determined by the treatment the patient had (sacubitril valsartan or enalapril) and patients' baseline characteristics, taken from the PARADIGM-HF trial. These were used to inform the number of hospitalisations occurring in the initial period of the economic analysis, but also allowed for extrapolation beyond the follow-up of the PARADIGM-HF trial. The rate of hospitalisation was assumed constant over time, therefore assuming that hospitalisation was not related to disease progression over time.

3.21 In the company's primary base case analysis, transition probabilities between the alive and dead health states were taken from all-cause mortality data from PARADIGM-HF in the base

case. All-cause mortality was estimated with survival regression analysis. The company chose the Gompertz distribution for its base case, noting that its clinical experts considered it to be clinically plausible, that it provided the most conservative (shortest) estimate of survival benefit, and that it was used in NICE technology appraisal guidance on ivabradine for treating chronic heart failure'. Predicted all-cause mortality was determined by the treatment the patient had (sacubitril valsartan or enalapril) and patients' baseline characteristics, taken from the PARADIGM-HF trial. The mortality model was run using the full analysis set population of the PARADIGM-HF trial and the model outputs provided daily hazard rates. These were used to model the probability of patients dying in the initial period of the economic analysis but also allowed for extrapolation of mortality beyond the end of the PARADIGM-HF trial for the remainder of the modelled time horizon. In an alternative analysis, the company derived transition probabilities between the alive and dead health states from cardiovascular-related mortality. The Gompertz distribution was also used for this analysis.

3.22 The company used a linear mixed regression model based on EQ-5D trial data from PARADIGM-HF to predict the utility scores for patients in the base-case analysis. Since the economic model did not explicitly include mutually exclusive health states (other than the alive and the dead states), mean utility values over time were calculated for each patient profile. Predicted EQ-5D scores were based on which treatment the patient had, baseline characteristics (including baseline EQ-5D), and risk of hospitalisation and adverse events.

3.23 A small but statistically significant EQ-5D treatment effect in favour of sacubitril valsartan was assumed after controlling for the effects

of hospitalisations and adverse events. This was assumed to persist for the duration of the time horizon. EQ-5D scores were assumed to decline at a constant rate of −0.008 per year over the modelled time horizon (30 years), which was based on data from PARADIGM-HF and a longitudinal study by Berg et al. (2015) which reported an annual decline in EQ-5D of −0.006. The rate of decline was not dependent on baseline characteristics.

3.24 The company applied utility decrements when a patient was hospitalised, with a decrement of −0.105 during days 0 to 30, and −0.054 during days 30 to 90. The company also applied adverse event utility decrements for hypotension (−0.029) and cough (−0.028) over an average duration of 64.9 days and 73.3 days respectively. The effect of serious adverse events that needed hospitalisation on quality of life was assumed to be captured in the utility decrements associated with hospitalisation.

3.25 For the comparison of sacubitril valsartan with ARBs in the company's secondary base case analysis, all-cause mortality and all-cause hospitalisation models used the network meta-analysis results to estimate the effectiveness of sacubitril valsartan compared with candesartan. For the all-cause hospitalisation model the company applied a hazard ratio of 0.90 for ARBs compared with ACE inhibitors (that is, candesartan was assumed to be 10% more effective than enalapril in preventing hospitalisations). Utility values in the ARB treatment arm of the model were assumed to be equivalent to the ACE inhibitor treatment arm as modelled in the primary base-case analysis.

3.26 Adverse events included in the base-case model were based on the full analysis set population rather than the safety analysis set. The company stated this was to ensure consistency with the modelling of clinical and quality of life outcomes, which were also

based on the full analysis set population. The company modelled the adverse events by assuming a constant probability of a specific adverse event occurring each cycle. It assumed that all-cause hospitalisation included all the relevant serious adverse events, including the associated costs and impact on patients' quality of life. The adverse events in the trial designated non-serious were modelled independently from hospitalisation. These were hypotension, elevated serum creatinine, elevated serum potassium, cough and angioedema. Adverse events in the secondary analysis in the ARB treatment arm of the model were assumed to be equivalent to the sacubitril valsartan treatment arm.

3.27 Resource use and costs considered in the model included:

- intervention and comparator costs (including background therapies)
- treatment initiation costs
- hospitalisation costs
- heart failure management costs
- adverse event costs.

3.28 The company based the daily costs of ACE inhibitors and sacubitril valsartan on observed doses from PARADIGM-HF. The cost of hospitalisation was based on healthcare resource groups mapped from physician-reported diagnoses, surgeries and interventional procedures that could be classified, and medical management hospitalisations with more than 30 instances considered. Typical costs of standard care (including beta blockers and aldosterone antagonists) and background medications were based on recommended doses. Estimates of background resource use, including emergency department referrals, outpatient contacts and GP visits, were taken from relevant national sources. A Clinical

Practice Research Datalink (CPRD) analysis commissioned by the company in order to characterise the burden of illness in the UK for patients with heart failure was used as the main source for resource use in the base case.

3.29 The primary base-case deterministic incremental cost effectiveness ratio (ICER) for sacubitril valsartan compared with ACE inhibitors was £17,939 per QALY gained (representing incremental costs of £7514 and incremental QALYs of 0.42), and the probabilistic ICER was £18,818 per QALY gained. The probabilities of sacubitril valsartan being cost-effective at thresholds of £20,000 and £30,000 were 64% and 93% respectively.

3.30 Deterministic one-way sensitivity analysis showed that for the comparison with ACE inhibitors the ICER was most sensitive to all-cause mortality, with the greatest effects on the ICER coming from the treatment effect of sacubitril valsartan on all-cause mortality, the baseline risk of all-cause mortality, and age (as a result of its impact on expected survival). Variables which had a modest effect included the improvements in health-related quality of life and reduction in hospitalisations.

3.31 The company carried out deterministic scenario analyses for the comparison of sacubitril valsartan with ACE inhibitors. The scenarios associated with ICERs over £30,000 per QALY gained were if the sacubitril valsartan treatment effect were assumed to persist for less than 5 years and if the modelled time horizon was reduced to less than 5 years.

3.32 For the company's secondary base case analysis of sacubitril valsartan compared with ARBs, the deterministic ICER was £16,481 per QALY gained (representing incremental costs of £8513 and incremental QALYs of 0.52) and the probabilistic ICER

was £17,599 per QALY gained. The probabilities of sacubitril valsartan being cost-effective at thresholds of £20,000 and £30,000 were 60% and 77% respectively. Results of the one-way deterministic sensitivity analysis were consistent with the analysis comparing sacubitril valsartan with ACE inhibitors, except the all-cause mortality hazard ratio for ARB compared with ACE inhibitors from the network meta-analysis was the most influential parameter. This parameter was subject to a high degree of uncertainty as a result of the wide credible intervals generated by the network meta-analysis (see section 3.39 of the ERG critique).

3.33 The company also presented results obtained using cardiovascular mortality (rather than overall mortality in the base case). In this case, the deterministic ICERs for sacubitril valsartan were £16,678 per QALY gained compared with ACE inhibitors and £16,569 per QALY gained compared with ARBs.

ERG critique of the company's submission

Clinical effectiveness

3.34 The ERG commented that the PARADIGM-HF trial was well conducted and that most patients in the trial were taking beta blockers as concomitant therapies, which reflected UK clinical practice. However, the ERG had the following concerns:

- The ERG noted that the population from the trial had a mean age of 63.8 years and that 32% of patients were less than 55 years old. It stated that in routine clinical practice average age would be much higher, at between 76 years (men) and 80 years (women). The ERG also noted that the trial included a lower proportion of women (about 22%) than in UK clinical practice. The ERG was advised by its clinical experts that these patient characteristics were associated with improved outcomes,

although it also noted that this effect would be observed across both treatment arms of the trial.

- The ERG was advised by its clinical experts that the cardiac device use observed at baseline in the trial was lower than is typical in UK clinical practice.

3.35 The ERG was advised by its clinical experts that the dose of valsartan (in sacubitril valsartan) in the PARADIGM-HF trial was higher than that typically prescribed in UK clinical practice. The ERG noted that the target dose of sacubitril valsartan was 200 mg twice daily, of which 103 mg is valsartan, which is equivalent to a 160 mg dose of valsartan given alone. The ERG noted that this dose was, according to the summary of product characteristics, the maximum dose allowed in clinical trials for valsartan monotherapy. According to clinical expert opinion provided to the ERG it is uncommon for patients to tolerate such high doses of valsartan in UK clinical practice. The ERG noted several factors that were likely to have contributed to the increased tolerability of valsartan in the trial:

- At baseline, around 78% of patients were taking an ACE inhibitor and around 23% of patients were taking an ARB.
- Around 70% of patients had been diagnosed with heart failure for over 1 year.
- The minimum tolerability inclusion criterion in the PARADIGM-HF protocol defined a minimum tolerable dose of valsartan (160 mg daily), which appears to be higher than the average dose tolerated by patients in UK clinical practice.
- Patients in the trial did not have any serious co-morbidities and death was included as a reason for discontinuation in both the trial and the CPRD analysis.

The ERG stated that the higher dose of valsartan tolerated by patients in the trial had an impact on the observed discontinuation of study drugs, which it suggested was likely to be higher in UK clinical practice than it was in the trial.

3.36 The ERG also had concerns over the comparison with enalapril because it was not representative of UK clinical practice. The company stated that enalapril was chosen because it is the ACE inhibitor that has been studied in the largest number of trials of patients with heart failure and it has a well-documented mortality benefit. However, the ERG's clinical experts advised that, in the UK, the most commonly used ACE inhibitor is ramipril. The ERG analysed the CPRD data commissioned by the company which showed that ramipril is the most commonly used ACE inhibitor in the UK. Therefore, the ERG stated that comparing sacubitril valsartan with enalapril did not reflect UK clinical practice.

3.37 The ERG considered the Western Europe population to be the most representative of the UK (24% of patients in PARADIGM-HF were from Western Europe). Clinical expert opinion sought by the ERG suggested that heart failure can have different causes across different geographical regions. The ERG also noted that the place of care was likely to have an effect on the use of medical devices; for example, implants are more likely to be seen in Western Europe and North America than in Latin America. In response to the clarification questions, the company provided the baseline characteristics of patients in the trial who were part of the Western European population (n=2057). The ERG noted that sacubitril valsartan was associated with a favourable but non-statistically significant difference in the Western Europe subgroup for the primary composite outcome, as well as in terms of both cardiovascular and all-cause mortality. It considered that this may

be because people in this subgroup have lower blood pressure, less severe heart failure and more intensive 'standard care' (as indicated by a slightly higher consumption of ACE inhibitors). The ERG concluded that the effect of sacubitril valsartan observed in the trial population may not be observed when used in clinical practice in the UK.

3.38 The ERG considered the results from the PARADIGM-HF and TITRATION trials in relation to the company's proposed positioning of sacubitril valsartan in the treatment pathway. The ERG's clinical experts indicated that based on the PARADIGM-HF trial design, population and outcomes, the evidence best supported sacubitril valsartan as a second-line treatment option for patients who are still symptomatic despite taking an ACE inhibitor. The ERG did not agree that the company's first-line positioning of sacubitril valsartan was reflected in the clinical trial evidence base for several reasons:

- The ERG felt the trial population did not reflect a newly diagnosed population.
- The ERG commented that the mortality in the PARADIGM-HF trial portrayed a scenario representative of the use of sacubitril valsartan in patients whose disease is established. It noted that less than 10% of patients in the trial had died by the end of year 1 and 20% were dead in both treatment arms by the end of year 2. The ERG contrasted this with the prognosis in NICE's guideline on chronic heart failure in adults: management 30% to 40% of patients diagnosed with heart failure die within a year. The ERG stated that this reinforced its view that the evidence presented in the company submission was most applicable to the use of sacubitril valsartan as a second-line treatment option, given to patients who are still symptomatic despite taking an ACE inhibitor.

- Because the patients in PARADIGM-HF were symptomatic despite having ARBs and ACE inhibitors, the ERG noted that the impact of continuing these patients on ACE inhibitors was likely to misrepresent what would happen in treatment-naïve patients. It further stated that, in principle, the ACE inhibitor treatment regimen has been demonstrated to not improve these patients' symptoms, and therefore randomising them to the same treatment regime is unlikely to show any improvements. The ERG suggested that this has an impact on the observed relative effectiveness of sacubitril valsartan, which may be overestimated in the trial population when compared with treatment-naïve patients.

3.39 The ERG noted that the company used methods for the network meta-analysis that were in line with the NICE Decision Support Unit's Technical Support Document 2. It also noted that, across all outcomes (all-cause mortality, cardiovascular mortality and all-cause hospitalisation) there were no hazard ratios from the network meta-analysis in which the credible intervals could be considered statistically significant. The ERG commented that the wide range of drug doses used to manage heart failure and the differences in NYHA classification of patients recruited to the trials in the network meta-analysis were sources of clinical heterogeneity which may have resulted in the wide credible intervals. Overall, the ERG regarded the results of the network meta-analysis conducted by the company to be uncertain and potentially unreliable based on the clinical heterogeneity in the trials underpinning the network.

3.40 The ERG stated the Cochrane systematic review by Heran et al. that the company had referenced in its assumption of a class effect for ARBs. It noted that the Cochrane review included some trials in which the population studied was not within the scope issued by

NICE (for example, because the patients included had heart failure with preserved ejection fraction). The ERG noted that there were similar results observed between the company's network meta-analysis and the meta-analysis from the Cochrane review, and stated that this gave some reassurance that the results were valid. However, it commented that the results needed to be interpreted with caution because of the inclusion in both meta-analyses of populations that were not within the scope issued by NICE.

3.41 Based on the ERG's concerns regarding the company's positioning of sacubitril valsartan as a first-line treatment, the ERG considered that the clinical effectiveness of sacubitril valsartan compared with ARBs in newly diagnosed patients with heart failure remained uncertain.

Cost effectiveness

3.42 The ERG stated that the formulae within the economic model were generally sound and that the economic model was a good predictor of the PARADIGM-HF trial outcomes. It also commented that the company had conducted scenario and subgroup analyses that were not requested in the NICE final scope but which added value to the submission. The ERG considered the use of a patient-level approach adopted by the company. The ERG stated that a patient-level approach was not completely justifiable in this case, and believed that the company should have provided more details and a clear justification as to why this approach taken.

3.43 Since the model population was based on the population of the PARADIGM-HF trial, the ERG reviewed how well the population reflected UK clinical practice (the ERG also reviewed this in its critique of the clinical effectiveness evidence for sacubitril valsartan; see sections 3.34, 3.35 and 3.37):

- The ERG considered mean age at baseline, and noted that NICE's guideline on chronic heart failure in adults: management states that 30% to 40% of people diagnosed die in the first year, but thereafter the mortality is less than 10% per year. Based on this, the ERG suggested that the starting age of patients in the economic analysis was a key factor. The ERG constructed hypothetical survival curves for mortality based on patients entering the model at 64 years old or 75 years old. Comparing the difference in the areas under the superimposed survival curves, the ERG demonstrated that there were considerable survival gains over time for the younger population, and this had implications for the costs and benefits collected during that time.
- The ERG was uncertain if the effectiveness of sacubitril valsartan in preventing hospitalisation differed across different age groups. The ERG discussed a study by Jhund et al. (2015) which concluded that the effect of sacubitril valsartan compared with enalapril was consistent across age groups, even though hazard ratios were non-statistically significant in older groups. The ERG suggested that the non-statistically significant result in older people was consistent with expert opinion advising that for patients who are around 80 years old, clinicians expect treatment to improve patients' quality of life but not mortality. The ERG commented that this was particularly relevant to the UK given that the average age of patients seen in clinical practice is between 75 and 80 years.
- Although the company positioned sacubitril valsartan as a first-line treatment in newly diagnosed patients, the population in the PARADIGM-HF trial was not reflective of newly diagnosed patients with heart failure seen in UK clinical practice.
- The target dose of valsartan (in sacubitril valsartan) in the PARADIGM-HF trial was the maximum dose allowed for

valsartan. However, the ERG stated that it seems to be uncommon for patients to tolerate such high doses of valsartan in clinical practice (see section 3.35). This has an impact on the observed discontinuation of study drugs, which is likely to be higher in UK clinical practice than in the trial.

- The ERG's clinical experts advised that heart failure can have different causes across different geographical regions. It was also noted by the ERG that there is likely to be variation in medical device use across regions (see section 3.39). The ERG's clinical experts also advised that differences in mortality across North America, Western Europe and the UK could be expected given that the UK has previously used fewer implantable cardioverter-defibrillators than the rest of Europe or North America.
- The ERG's clinical experts advised that the cardiac device use observed at baseline in PARADIGM-HF was lower than what would be expected in UK clinical practice and that the use of devices at baseline is an important prognostic factor for heart failure.

3.44 The ERG discussed the modelled treatment regimens. It stated that these broadly reflected the PARADIGM-HF trial, even though there was some inconsistency in the chosen treatment doses (see section 3.52). The ERG was concerned with how representative the modelled treatment regimens were of clinical practice. It noted that the modelled dose of sacubitril valsartan of 400 mg per day was unlikely to accurately represent the average dose of valsartan tolerated typically observed in clinical practice (see section 3.35). The ERG also noted that the dose of the ARB, candesartan, modelled in the economic analysis (32 mg daily) was different to the average dose reported in the CPRD analysis (around 10 mg per day during the follow-up period) and the observed daily mean

dose of candesartan in UK clinical practice (around 16 mg according to clinical experts). Finally, the ERG noted a discrepancy in the observed average daily dose for enalapril of 18.9 mg in the PARADIGM-HF trial compared with the CPRD data of about 16.5 mg. The ERG stated that the difference in intervention doses compared with clinical practice had an impact on the observed discontinuation of study drugs. The ERG noted that the base-case economic model did not consider drug discontinuation, but the company had carried out a scenario analysis in which the inclusion of discontinuation over the lifetime time horizon had only a modest impact on the ICER.

3.45 The ERG reiterated that the modelled population did not reflect patients typically observed in clinical practice or a newly diagnosed population, both of which would affect mortality in the model. The ERG did not run any additional analyses to try and replicate the mortality of newly diagnosed patients because too many assumptions would have had to be made to approximate a treatment-naïve population.

3.46 The ERG noted that the company's decision to use a Gompertz distribution was based on this distribution presenting the most plausible survival time. The ERG noted the company had not tried other approaches than parametric curves, and suggested that different modelling options, such as spline models, would have been useful. Even though the Gompertz distribution produced the most plausible survival curves among the group of alternative distributions considered, the ERG considered that it could represent an overestimate of treatment effects compared with different approaches.

3.47 The ERG discussed the company's use of the all-cause mortality model in the base case, as opposed to the use of cardiovascular

mortality. The company had chosen the all-cause mortality model because it was considered the most conservative approach (that is, it produced the higher ICER). The ERG commented that the cardiovascular mortality approach was likely to have been more robust. It stated that there were issues in using an all-cause mortality approach because it included non-cardiovascular mortality observed in the trial. Clinical experts explained that non-cardiovascular mortality was likely to be overestimated in the trial (compared with UK life tables) given that the trial included a considerable proportion of patients from countries where other causes of death, such as infection, are more prevalent than in Europe and North America.

3.48 The ERG commented that even though the modelled effect of age at baseline in cardiovascular mortality seems to be appropriate to capture the PARADIGM-HF trial data, the unexpected shape of the mortality curve leads to other issues in the economic analysis, such as the lack of face validity of the predicted life expectancy in the model. The ERG highlighted that the mortality survival model made some implausible predictions, such as 21-year olds having the same life expectancy as 87-year olds 72-year olds having a much higher life expectancy than 18-year olds. The ERG appreciated that this was a direct implication of the modelled effect of age at baseline on cardiovascular mortality, which in turn was a direct consequence of the PARDIGM-HF trial data.

3.49 The ERG was concerned with the validity of the company's health-related quality-of life analysis. Firstly, the ERG could not be certain whether there was a baseline statistically significant difference in patients' EQ-5D scores between the 2 treatment groups of sacubitril valsartan and enalapril. It suggested the statistical test performed by the company that found there was no statistically

significant difference might not be appropriate. Secondly, the ERG stated that the trial and consequently the model outcomes could potentially be biased if there was a clinically significant difference in patients' disease severity and quality of life across the treatment groups. The ERG suggested that, assuming patients in a healthier state would have better outcomes, the potential imbalance in disease severity might have favoured the sacubitril valsartan group.

3.50 For the secondary base case analysis of sacubitril valsartan compared with ARBs, the ERG was concerned with the clinical heterogeneity in the trials underpinning the network meta-analysis. It considered that the clinical effectiveness of sacubitril valsartan compared with ARBs in patients newly diagnosed with heart failure remained an unanswered question.

3.51 Regarding the company's use of CPRD data for estimating resource use, the ERG agreed with the company that such real-world data was more robust and more reflective of the UK population than literature studies. However, the ERG was concerned with the appropriateness of using CPRD data to estimate the resource use for the patient profiles observed in the trial because there were differences in the 2 populations.

3.52 The ERG noted that the company's assumptions of daily drug doses were not consistent across different treatments. For some treatments, the doses were estimated as the average between the minimum and maximum dose; for others, the doses were based on maximum doses. The ERG carried out an exploratory analysis to reflect consistent drug dose assumption and using the cost of ramipril instead of enalapril. Based on advice from its clinical experts, it assumed a reduced cost for ramipril reflecting the fact that in clinical practice ramipril is given as a single daily dose, rather than as 2 daily doses.

3.53 The ERG stated the hospitalisation cost would be expected to depend on starting age and time. The ERG's clinical experts advised that the incidence of hospitalisation caused by renal failure in the trial appeared to be lower than expected, and that the cause could be as a result of the population being younger and healthier than in UK clinical practice. The ERG therefore had concerns that the starting age in the model impacted the cost savings caused by the reduction in hospitalisations.

3.54 The ERG was concerned that the company had not appropriately accounted for parameter uncertainty in the economic analysis. The ERG stated that patients' baseline characteristics should have been included in the deterministic and probabilistic sensitivity analyses, given the concerns regarding the lack of generalisability of the PARADIGM-HF trial population to clinical practice. The ERG also commented that the baseline characteristics were key parameters in the economic model given that these were included as prognostic factors of mortality, hospitalisation, quality of life and costs in the regression analyses.

ERG exploratory analyses

3.55 The ERG's scenario analyses were done in populations with a mean starting age of 64 years (as per the company's base case reflecting the clinical trial) and a mean starting age of 75 years (to better reflect the UK heart failure population). The ERG used cardiovascular mortality and average patient characteristics in each cohort (as opposed to all-cause mortality and the use of patient-level characteristics in the company's primary and secondary base case analyses).

3.56 The ERG's scenario analyses in the 64-year-old population included the following changes to the company's primary base case model:

- The ERG explored a change in the cardiovascular mortality hazard ratio to reflect the Jhund et al. point estimate and confidence interval limits for the 55- to 64-year category. The hazard ratio used was 0.79 (CI 0.64 to 0.98).
- The ERG used the baseline utility score of 0.
- The ERG explored alternative baseline utility values, using a utility value of 0.72 reported by Berg et al. and, in another scenario analysis, using a utility value of 0.66 as reported by Austin et al.
- The ERG explored the use of a simplified approach to modelling quality of life. The impact of sacubitril valsartan on patients' quality of life was linked to the incidence of adverse events and hospitalisation events and disease progression in both treatment arms. Therefore, the quality of life regression model was not used (although some estimates were taken from it because they had been validated by clinical experts). The impact of sacubitril valsartan alone on quality of life was also removed to reflect the lack of robust evidence to support a measurable improvement in patients' quality of life caused by sacubitril valsartan other than through hospitalisation, mortality and adverse events. The ERG assessed the treatments' effect on quality of life through:
  - adverse events and hospitalisation events (applying the same utility decrements used by the company to estimate the loss in quality of life due to the incidence of adverse events and hospitalisation)
  - disease progression (applying the same utility decrement used by the company to reflect the loss of quality of life as time progressed).

- The ERG explored changing the drug doses used in the model to reflect a consistent approach to the estimation of drug costs.
- The ERG included the cost of ramipril (using the ERG drug dose assumption of a single daily 5 mg dose) to reflect clinical practice in the UK.
- The ERG used the option included in the company's economic model to run the ERG-corrected model considering treatment discontinuation.
- The ERG explored using the company's subgroup analysis results to run the ERG-corrected model considering the Western European population.

3.57 The ERG's scenario analyses in the 75-year-old population included the following:

- The ERG changed the cardiovascular mortality hazard ratio in the model to reflect the Jhund et al. point estimates and confidence interval limits for the ≥75 year-old category. This HR (0.84, 95% CI 0.67 to 1.06) was non-statistically significant, so the ERG ran the model with a hazard ratio of 1.

3.58 The ERG noted its additional analyses for the 64-year old and 75-year old populations were consistent with the company's sensitivity analysis in showing that the model results were relatively robust but were most sensitive to changes in the mortality hazard ratio, with cardiovascular mortality the key model driver.

3.59 The ERG presented ICERs for sacubitril valsartan compared with enalapril assuming that sacubitril valsartan was used as a second-line treatment in clinical practice. The ICERs estimated by the ERG were based on the PARADIGM-HF population and clinical effectiveness results. The ERG used the following assumptions:

- mean starting age of 75 years
- baseline utility value taken from Berg et al.
- using the cost of ramipril instead of enalapril to reflect clinical practice in the UK
- using the effectiveness outcomes, costs, QALYs and population characteristics of the Western European subgroup analysis.
- using an alternative quality of life modelling approach (see section 3.61) and adjusted drug costs to reflect target doses consistently across the economic analysis.

3.60 The second-line ICERs estimated by the ERG are presented in Table 1.

Table 1 ERG's estimated ICERs: second-line treatment

Results per patient	Sacubitril + SoC	Enalapril + SoC	Incremental value
Company's base case with ERG corrections			
Total costs (£)	£22,961	£14,308	£8,653
QALYs	5.40	4.82	0.58
ICER			**£15,026**
Mean age at baseline of 75 years			
Total costs (£)	£19,498	£12,562	£6,936
QALYs	4.43	3.99	0.44
ICER (compared with base case)			**£15,843**
ICER with all changes incorporated			**£15,843**
Change in baseline utility to reflect Berg et al utility (0.72)			
Total costs (£)	£22,824	£14,299	£8,525
QALYs	5.11	4.55	0.55
ICER (compared with base case)			**£15,407**
ICER with all changes incorporated			**£16,190**
Change in QoL modelling approach			
Total costs (£)	£22,961	£14,308	£8,653
QALYs	5.30	4.80	0.50
ICER (compared with base case)			**£17,413**
ICER with all changes incorporated			**£19,697**
Change in pharmaceutical costs to reflect drug target doses			
Total costs (£)	£23,085	£14,430	£8,655
QALYs	5.40	4.82	0.58
ICER (compared with base case)			**£15,030**
ICER with all changes incorporated			**£19,701**
Change in pharmaceutical costs to reflect the cost of ramipril			
Total costs (£)	£22,961	£14,257	£8,704
QALYs	5.40	4.82	0.58
ICER (compared with base case)			**£15,115**
ICER with all changes incorporated			**£19,843**
Western Europe subgroup			
Total costs (£)	£24,182	£17,341	£6,841
QALYs	4.86	4.52	0.33

ICER (compared with base case)		**£20,550**
ICER with all changes incorporated		**£29,478**
Abbreviations: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; SoC, standard of care; QALYs, quality-adjusted life years; QoL, quality of life.		

3.61 The ERG estimated a second line ICER for sacubitril valsartan compared with ARBs of £30,140 per QALY gained. Noting its previous concerns, the ERG considered that its ICERs must be interpreted with caution because of uncertainty around the effectiveness of sacubitril valsartan compared with enalapril when analysed in the context of UK clinical practice. The ERG also presented further scenario analyses which demonstrated the variance in values when different hazard ratios and mortality approaches (cardiovascular or all-cause) were taken. In these analyses, the ICERs for sacubitril valsartan compared with ACE inhibitors ranged from £14,942 per QALY gained to being dominated (that is, ACE inhibitors were both more effective and less costly).

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of sacubitril valsartan, having considered evidence on the nature of chronic heart failure with reduced ejection fraction and the value placed on the benefits of sacubitril valsartan by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1 The Committee considered the clinical need for people with chronic heart failure who are covered by the marketing authorisation of sacubitril valsartan. The Committee heard from the clinical experts that people with chronic heart failure have a poor quality of life. It

heard from the patient experts that chronic heart failure can impact on everyday tasks, with comorbidities increasing the impact of the disease and usually requiring lifestyle changes. It also heard from the patient experts that angiotensin-converting enzyme (ACE) inhibitors have been the gold standard treatment for almost 25 years, and that a new treatment option would provide hope and generate optimism. The Committee recognised the impact of chronic heart failure on quality of life and concluded that there were treatment benefits with sacubitril valsartan for people who are covered by the marketing authorisation.

4.2 The Committee considered the current treatment pathway for people with chronic heart failure, and the position in the pathway for sacubitril valsartan. It noted that sacubitril valsartan has a marketing authorisation for 'the treatment of symptomatic chronic heart failure with reduced ejection fraction', and therefore includes patients who have and who have not previously received treatment with ACE inhibitors or ARBs. The Committee heard from the clinical experts that clinical practice is broadly in line with the NICE guideline on chronic heart failure in adults: management in that ACE inhibitors are the gold standard initial treatment and are taken concomitantly with a beta blocker and an aldosterone antagonist. The clinical experts stated that angiotensin II receptor-blockers (ARBs) were also used in clinical practice for people who cannot take ACE inhibitors with concomitant beta blockers and an aldosterone antagonist. The Committee discussed whether sacubitril valsartan would be given to patients who were newly diagnosed with chronic heart failure or only to those who were already taking an ACE inhibitor or an ARB. The Committee heard from the clinical experts that 40 to 50% of patients with newly diagnosed heart failure may already be receiving an ACE inhibitor for other conditions (for example, hypertension). The clinical

experts stated that they are likely to offer sacubitril valsartan to people who are newly diagnosed with chronic heart, but who are already receiving an ACE inhibitor or an ARB. The clinical experts explained that they would be reluctant to give sacubitril valsartan to people who had not previously received ACE inhibitors or ARBs because of the lack of evidence for clinical effectiveness and safety of sacubitril valsartan in this population. The Committee agreed there was a lack of evidence for people who were treatment naïve, to ACE inhibitors or ARBs noting that 99% of patients in the PARADIGM-HF trial were taking ACE inhibitors or ARBs at entry to the study. The Committee agreed that the most appropriate position in the treatment pathway for sacubitril valsartan would be for people who are already receiving a stable, optimised dose of an ACE inhibitor or an ARB along with standard therapy of beta-blockers and aldosterone antagonists. The Committee concluded that sacubitril valsartan should only be offered to patients who are already taking a stable dose of ACE inhibitors or ARBs.

Clinical effectiveness

4.3 The Committee considered the generalisability of the PARADIGM-HF trial results to people diagnosed with chronic heart failure with reduced ejection fraction in England. It noted that people in the trial were younger, included a higher proportion of men, were less likely to be using cardiac devices, and had greater tolerability to valsartan (in sacubitril valsartan). The clinical experts acknowledged these differences between the trial population and patients typically seen in clinical practice in England, and stated that the differences would not affect the way they prescribe sacubitril valsartan because the inclusion criteria used in the trial were common to all randomised trials in this disease area. The clinical experts acknowledged that the dose of sacubitril valsartan was roughly twice the dose that

would be normally tolerated in clinical practice, and that this suggested the treatment would be less effective in clinical practice than in the trial because of the dose-dependent nature of the treatment. However, the clinical experts commented that the dose of enalapril in the trial was also greater than would be typically observed in clinical practice, and that they would therefore expect these differences to cancel each other out, such that the relative treatment effect between sacubitril valsartan and ACE inhibitors in clinical practice to be similar to that in the trial. The Committee noted comments from the ERG that the most appropriate choice of ACE inhibitor comparator was ramipril rather than enalapril. It heard from clinical experts that enalapril has the largest evidence base for its effectiveness, but that ramipril is more commonly used in clinical practice. The Committee noted that the company had assumed a class effect for ACE inhibitors, based on the findings of a systematic review and network meta-analysis (Chatterjee et al. 2013). It agreed a class effect for ACE inhibitors was an appropriate assumption, and that the choice between enalapril and ramipril therefore only affected the costs used in the economic modelling. The Committee agreed that the generalisability was similar across all trials in this condition, and it concluded that, despite the differences between the trial and the trial eligible population in England, the results of the PARADIGM-HF trial were relevant to established clinical practice in England.

4.4 The Committee examined the clinical effectiveness evidence from PARADIGM-HF comparing sacubitril valsartan with enalapril. The Committee considered the PARADIGM-HF trial was a good quality trial and that the relevant clinical outcomes of mortality and hospital admission were assessed. The Committee noted that in the total trial population, the composite primary end point (death from cardiovascular causes or a first hospitalisation for worsening heart

failure) significantly favoured sacubitril valsartan compared with enalapril (hazard ratio [HR] 0.80; 95% confidence interval [CI] 0.73 to 0.87, p<0.001). It heard from the clinical experts that such a benefit was considered to be clinically significant. The Committee also noted that sacubitril valsartan was associated with a statistically significant benefit compared with enalapril in each of the separate components of the primary end point, and was also associated with a statistically significantly reduced risk of all-cause mortality (see section 3.7). The Committee concluded that, for the population included in the PARADIGM-HF trial, sacubitril valsartan was statistically significantly more clinically effective than enalapril at reducing hospitalisations and improving both overall mortality and cardiovascular mortality.

4.5 The Committee considered the subgroup analyses presented by the company. It noted that the company had submitted a large number of prespecified subgroup analyses, and that across all groups sacubitril valsartan was consistently better than ACE inhibitors with regard to the primary end point. The Committee was aware that the treatment effect for several subgroups did not reach statistical significance, including the Western Europe group (HR 0.89, 95% CI 0.74 to 1.07), the group who were aged 75 years or older (HR 0.86, 95% CI 0.72, 1.04), the group with NYHA class III or IV heart failure (HR 0.92, 95% CI 0.79, 1.08), and the group who had not previously had ACE inhibitors (HR 0.92, 95% CI 0.76 to 1.10). The Committee was aware that the Western European subgroup analysis was a post-hoc analysis because it excluded Israel and South Africa (which had been included for operational reasons in the prespecified Western Europe subgroup). The Committee understood that for all the subgroups, including the Western Europe subgroup which represented 24% of the total trial population, the comparisons were not powered to detect

statistically significant differences in the primary end point, and that the hazard ratio point estimates all suggested a benefit in the sacubitril valsartan group. The Committee heard from clinical experts that the lack of statistically significant outcomes among certain subgroups did not affect their assessment of the drug's effectiveness. The Committee considered the tests of interaction carried out by the company which showed little evidence of treatment-effect modifiers for most subgroups. The Committee considered that because the results of subgroup analyses were consistently positive, any differential interpretation of treatment effect in subgroups should be undertaken with caution. The Committee noted that the ERG had considered the Western Europe subgroup to be the most representative of clinical practice in England. It understood that the ERG based this on the race, age and cardiac device use of the Western Europe subgroup (baseline characteristics of the Western Europe subgroup were designated academic in confidence by the company). The Committee agreed that patients in this group were more comparable to patients in clinical practice in England compared with the total trial population.. It concluded that the Western Europe subgroup was the most representative of clinical practice in England, but that the lack of statistical significance associated with certain subgroups would not factor in its decision-making and it would therefore focus on the point estimate results in these subgroups.

4.6 The Committee noted that there were no head-to-head trials comparing sacubitril valsartan with ARBs, and therefore considered the network meta-analysis carried out by the company to estimate the relative treatment effect for sacubitril valsartan compared with ARBs. The Committee noted that the results from the network meta-analysis suggested that ARBs and ACE inhibitors were broadly equivalent, and that sacubitril valsartan was superior to

ARBs with regards to all-cause and cardiovascular mortality and broadly equivalent with regards to all-cause hospitalisation. The Committee considered the network meta-analysis to be methodologically sound, noting that it used methods that were in-line with the NICE Decision Support Unit's Technical Support Document 2. However, it was aware of the issues raised by the ERG with regard to heterogeneity in the trials underpinning the network, and with regard to the wide confidence intervals associated with the results of the network meta-analysis. It understood that the company's network meta-analysis reflected the approach taken by the Cochrane meta-analysis by Heran et al. (2012), and that both analyses had provided similar results. Overall, the Committee concluded that although the results of the network meta-analysis should be treated with caution, the consistency of findings between the network meta-analyses by Heran et al. and the company provided sufficient reassurance that the results were valid, and were appropriate for the purposes of decision-making regarding the clinical effectiveness for sacubitril valsartan compared with ARBs.

4.7 The Committee considered the adverse event profile associated with sacubitril valsartan compared with enalapril. It considered that the overall safety profiles during the double-blind trial period of PARADIGM-HF were comparable between the 2 treatment groups, and noted that there were no statistically significant differences with regard to discontinuations because of adverse events. The Committee noted that the sacubitril valsartan group had statistically significantly higher rates of hypotension than the enalapril group, with a particularly large hazard ratio of 1.48. The Committee considered the potential consequences of the increased rate of hypotension, for example injuries from falls, particularly as the age of patients in clinical practice is higher than the trial population.

However, the Committee understood that hypotension was related to the greater vasodilator effect of sacubitril valsartan, and noted that there was no increase in the rate of discontinuation because of possible hypotension-related adverse events. The Committee concluded that sacubitril valsartan had a manageable adverse event profile in the population specified in the marketing authorisation.

4.8 The Committee explored what left ventricular ejection fraction level was required for sacubitril valsartan to be considered an appropriate treatment option for people with chronic heart failure. It was aware that an ejection fraction level was not specified in the marketing authorisation for sacubitril valsartan. However, it considered that sacubitril valsartan could not be recommended in people with a left ventricular ejection fraction that is above 35% because the left ventricular ejection fraction entry criterion for the PARADIGM-HF trial was changed from 40% or less to 35% or less. The Committee discussed how the ejection fraction level will be determined in clinical practice and whether the required tests will be readily available to people who will potentially benefit from sacubitril valsartan. It was aware that ejection fraction level is usually demonstrated with an echocardiogram and additional tests will not necessarily be required before initiating sacubitril valsartan. The Committee concluded that sacubitril valsartan should only be initiated in people with an ejection fraction of 35% or less, normally shown on an echocardiogram.

4.9 The Committee explored what NYHA class was required for sacubitril valsartan to be considered an appropriate treatment option for people with chronic heart failure. It was aware that NYHA class was not specified in the marketing authorisation for sacubitril valsartan. The Committee noted that the inclusion criteria for the

PARADIGM-HF trial specified patients with NYHA class II-IV. The Committee was also aware that over 90% of the people who entered the PARADIGM-HF trial had a NYHA class of II and III and that less than 1% (n=60, 0.7%) had NYHA class IV heart failure. The Committee agreed that the representation of patients with NYHA class IV was limited and that the effectiveness of sacubitril valsartan was uncertain because of the small number of patients in the PARADIGM-HF trial. Therefore, the Committee concluded that sacubitril valsartan should only be initiated in people with NYHA class II or III chronic heart failure.

4.10 The Committee considered how sacubitril valsartan will be prescribed in clinical practice. It heard from clinical experts that a heart failure specialist in secondary care with access to a multidisciplinary team should initiate sacubitril valsartan. The clinical experts also stated that titration and monitoring of sacubitril valsartan could then take place in primary care by a GP with a special interest in heart failure or a heart failure specialist nurse, supported by a multidisciplinary team. They highlighted that this may help ensure that only appropriate patients have sacubitril valsartan. The Committee noted that the NICE guideline on chronic heart failure in adults: management defined a specialist as a physician with a subspecialty interest in the management of heart failure and who leads a specialist multidisciplinary heart failure team of professionals with appropriate competencies from primary and secondary care. The Committee also noted that the inclusion criteria of the trial specified that patients must have been taking a stable dose of an ACE inhibitor or an ARB for at least 4 weeks before entering the study. It recalled its previous discussions (see section 4.2) that that there was a lack of evidence for sacubitril valsartan in people who were treatment naïve to ACE inhibitors or ARBs, and it heard from clinical experts that sacubitril valsartan

would only be considered for people who are already receiving a stable, optimised dose of an ACE inhibitor or an ARB. The Committee concluded that sacubitril valsartan should be started by a heart failure specialist (in line with the NICE guideline) with access to a multidisciplinary heart failure team, in people who are receiving a stable, optimised dose of an ACE inhibitor or an ARB. It further concluded that dose titration and monitoring should then be carried out by a heart failure specialist or in primary care by either a GP with a special interest in heart failure or a heart failure specialist nurse.

Cost effectiveness

4.11 The Committee discussed the company's economic model and the ERG's critique of this model. It heard from the clinical experts that the model captured the outcomes that were clinically relevant to chronic heart failure. The Committee considered the company's model to be generally well structured, a good predictor of the PARADIGM-HF trial outcomes and noted it was of a similar structure to those previously published, including the model submitted during the development of NICE technology appraisal guidance on ivabradine for treating chronic heart failure. The Committee noted that the company's model made use of patient-level data in the base-case analysis, and that the ERG had considered this was not completely justifiable. It understood that the company had developed the model allowing the user to run it using average patient characteristics in each cohort, and that the ERG's exploratory analyses had been carried out using this alternative approach. The Committee considered there were advantages and disadvantages for both the patient-level and the cohort-model approaches, and it was aware that in this case similar model outcomes were observed for both modelling approaches.

The Committee therefore considered that both the cohort model using average patient characteristics and the patient-level approach were acceptable. The Committee concluded that the company's model was sufficiently robust for assessing the cost effectiveness of sacubitril valsartan.

4.12 The Committee considered the age of patients entering the economic model. It noted that the mean baseline age in the company's base case (64 years) reflected the PARADIGM-HF trial. It was aware that in exploratory analyses the ERG had adjusted the model to a mean baseline age of 75 years, and agreed that this more closely reflected the age of patients generally seen in clinical practice. It discussed the ERG's concerns that the modelling approach taken by the company resulted in an inflexible economic model, and that despite its adjustment to the baseline age, the model could not be changed to portray an older population at baseline and generalise the model results. It understood that the model was accurate in replicating the trial data, but that there were issues of face validity (see section 3.48). The Committee heard from clinical experts that these findings could not be explained from a clinical perspective, and the Committee agreed that there was some uncertainty as to whether the ERG's additional analysis in 75-year olds was fully reflective of the true cost-effectiveness of sacubitril valsartan in an older population. The Committee was aware that this issue was a result of the economic model being structured to closely reflect the population and outcomes from the PARADIGM-HF trial, but recalled that it had accepted that the results of the PARADIGM-HF trial were relevant to routine clinical practice for a trial-eligible population (see section 4.3). The Committee concluded that, despite the inflexibility of the company's economic model and the resulting constraints in generalising the model results to portray an older population, the ERG's use of a

baseline age of 75 years was a reasonable attempt to generalise the model results to the heart failure population in England, and was appropriate for the purposes of decision-making.

4.13 The Committee considered the population used in the economic model. It noted that the company had used the results of the full analysis set population to inform its model, and that in exploratory analyses the ERG had used only the company's Western Europe subgroup analysis results. The Committee recalled its earlier conclusions that the Western Europe subgroup was the most representative of clinical practice in England (see section 4.5), and it therefore considered the use of the results for this subgroup was more appropriate for the cost effectiveness analyses comparing sacubitril valsartan with ACE inhibitors and ARBs.

4.14 The Committee considered the modelling of health-related quality of life. It noted that the company used a linear mixed regression model based on EQ-5D trial data from PARADIGM-HF to predict utility scores. It further noted that the company had assumed a small but statistically significant EQ-5D treatment effect in favour of sacubitril valsartan even after controlling for the effects of hospitalisations and adverse events. The Committee considered the ERG's concerns, in particular that the trial (and consequently the model outcomes) could potentially be biased in favour of the sacubitril valsartan group if, for example, patients in this group had a better quality of life at baseline, and this healthier state may be carried through to the trial and result in better outcomes. The Committee noted that in exploratory analyses the ERG had explored changing the baseline utility value to reflect the utility value in the publication by Berg et al., and it had adopted a simplified quality of life modelling approach linked to the incidence of adverse events, hospitalisation events and disease progression

(see section 3.55). The Committee heard from clinical experts that hospitalisation rates were a good surrogate for determining patients' quality of life, and it understood that the ERG's simplified approach adequately captured the impact of reduced hospitalisation. The Committee agreed that the ERG's exploratory analyses in which it used a simplified approach to estimating quality of life and used a baseline utility from Berg et al. were both more appropriate than the company's primary base case (that is the comparison of sacubitril valsartan with ACE inhibitor [enalapril]) for the purposes of decision-making.

4.15 The Committee noted that the company had chosen to model enalapril as the ACE inhibitor comparator although ramipril is more commonly used in clinical practice (see section 4.3). The Committee noted that in its exploratory analyses, the ERG had included the cost of ramipril and assumed drug doses for ramipril that reflected the way it is given in clinical practice in the UK. This had only a modest impact on the incremental cost-effectiveness ratio (ICER), but the Committee agreed that the use of ramipril costs rather than enalapril costs more appropriately reflected clinical practice in England.

4.16 The Committee noted that the company's assumptions regarding the daily drug doses were not consistent across different treatments (see section 3.52). The ERG carried out exploratory analyses to reflect a consistent approach using target doses for estimating drug costs. The Committee noted that this change had almost no effect on the ICER, but concluded that a consistent approach to the use of drug doses was more appropriate to inform its decision-making.

4.17 The Committee considered the ICERs presented by the company for sacubitril valsartan compared with ACE inhibitors, as well as he

ERG's exploratory analyses. It noted that the company's base-case deterministic ICER for sacubitril valsartan compared with ACE inhibitors was £18,000 per quality-adjusted life year (QALY) gained (incremental cost £7,514, incremental QALY 0.42). The Committee noted that the company had done a number of scenario analyses that had shown the ICER was relatively robust to the changes explored. The Committee then considered the ERG's exploratory analyses. It noted that the ERG's exploratory analyses, including all of its preferred parameters or assumptions (see sections 4.10 to section 4.14), resulted in a deterministic ICER for sacubitril valsartan compared with ACE inhibitors of £29,500 per QALY gained (incremental costs £6,841, incremental QALYs 0.33). The Committee was aware that the ERG had considered its exploratory analyses to be associated with significant uncertainty because of the lack of generalisability of the results from the PARADIGM-HF trial and the lack of statistical significance associated with the Western Europe subgroup. The Committee recalled its conclusions that the lack of statistical significance associated with the treatment effect in the subgroups (in particular the Western Europe subgroup) would not factor in its decision-making because the point estimates were in the same direction and supported the estimates for the overall trial population (see section 4.5). The Committee considered the ERG's exploratory analyses to be the most appropriate analyses for its decision-making because they included all of its preferred assumptions, and concluded that the most plausible ICER for sacubitril valsartan compared with ACE inhibitors was £29,500 per QALY gained.

4.18 The Committee considered the ICERs for sacubitril valsartan compared with ARBs in people who cannot have an ACE inhibitor. It noted that the company's base-case deterministic ICER for sacubitril valsartan compared with ARBs was around £16,500 per

QALY gained (incremental costs £8,513, incremental QALYs 0.52). The Committee was mindful of its earlier conclusions that the results of the network meta-analysis were appropriate for the purposes of its decision-making (see section 4.6). It noted that for this analysis the ERG had presented equivalent exploratory analyses to the comparison with ACE inhibitors, and that these exploratory analyses included all of its preferred parameters or assumptions (see section 4.17) resulting in an ICER of £30,100 per QALY gained. The Committee concluded that the most plausible ICER for sacubitril valsartan compared with ARBs in people who cannot have an ACE inhibitor was £30,100 per QALY gained.

4.19 The Committee considered whether sacubitril valsartan was a cost-effective use of NHS resources. It was aware that the ICERs for the comparisons of sacubitril valsartan with ACE inhibitors and with ARBs were at the upper end of the range that would normally be considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained). The Committee was also aware that NICE's guide to the methods of technology appraisal states that above a plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the technology as an effective use of NHS resources will specifically take account of a number of other factors, including the innovative nature of the technology. The Committee recognised the innovative nature of sacubitril valsartan in that the inhibition of neprilysin is a novel development in the pharmacological management of heart failure. The Committee also considered comments from the clinical and patient experts that this is a disease area that has been historically underinvested. In addition, the Committee was aware that sacubitril valsartan has been granted a promising innovative medicine designation by the Medicines and Healthcare Products Regulatory Agency. The Committee concluded that sacubitril valsartan was innovative and

that it offered a small step-change in the management of this condition. The Committee considered that, given its innovative nature, the most plausible ICERs of £29,500 and £30,100 per QALY gained for sacubitril valsartan compared with ACE inhibitors and ARBs (for people who cannot have an ACE inhibitor) respectively, represented a cost-effective use of NHS resources. It considered that, given the issues of generalisability of the PARADIGM-HF trial to clinical practice in England (see section 4.3) the recommendations should closely reflect the population in the trial. The Committee noted that most patients in the trial were considered to have New York Heart Association (NYHA) class II or III heart failure at baseline, with less than 1% of patients having NYHA IV heart failure. It noted that the trial protocol had been amended from people with a left ventricular ejection fraction of 40% or less to people with a left ventricular ejection fraction of 35% or less. The Committee was also aware that the inclusion criteria of the trial specified that patients must have been taking a stable dose of an ACE inhibitor or an ARB (equivalent to enalapril 10 mg daily) for at least 4 weeks before entering the study. The Committee therefore considered that its recommendations should be restricted to people who fit these criteria and therefore recommended sacubitril valsartan as a cost effective use of NHS resources for treating chronic heart failure with reduced ejection fraction, only in people with NYHA class II to III chronic heart failure, who are already taking a stable dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor-blockers (ARBs) and have a left ventricular ejection fraction of 35% or less.

4.20 The Committee discussed whether there were any equality issues it should consider before making its recommendations. It noted the comments received during consultation had stated that there were higher rates of angio-oedema in those of African family origin

having ACE inhibitors, and that extra vigilance would be needed because of the low numbers of these patients included in the trial (5%). Bearing in mind that the Committee had recommended sacubitril valsartan, it concluded that there was no unfairness or unlawful discrimination and no need to alter or add to its recommendations.

4.21 The Committee considered whether it should take into account the consequences of the 2014 Pharmaceutical Price Regulation Scheme (PPRS), and in particular the PPRS payment mechanism, when appraising sacubitril valsartan. The Committee noted NICE's position statement in this regard, and accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The Committee heard nothing to suggest that there is any basis for taking a different view on the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not applicable when considering the cost effectiveness of sacubitril valsartan.

Summary of Appraisal Committee's key conclusions

TAXXX	**Appraisal title:**	**Section**
Key conclusion		
Sacubitril valsartan is recommended as an option for treating people with heart failure with reduced ejection fraction, only in people: • with New York Heart Association (NYHA) class II to III chronic heart failure and • if they are already taking a stable dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor-blockers		1.1 4.3 4.4 4.6

(ARBs) and • with a left ventricular ejection fraction of 35% or less. 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 done by the heart failure specialist, or in primary care by either a GP with a special interest in heart failure or a heart failure specialist nurse. The Committee was persuaded that despite the differences between the trial and the trial eligible population in England (such as younger age, less cardiac device use, and greater tolerability to treatments), the results of the PARADIGM-HF trial were relevant to routine clinical practice. It considered the issue of generalisability was similar across all trials in this condition. The Committee concluded that, for the population included in the PARADIGM-HF trial, sacubitril valsartan was statistically significantly more clinically effective than enalapril at reducing hospitalisations and improving both overall mortality and cardiovascular mortality. The Committee concluded that the results of the network meta-analysis were appropriate for the purposes of decision-making regarding the clinical effectiveness for sacubitril valsartan compared with ARBs. The Committee considered the ERG's exploratory analyses to be the most appropriate analyses for its decision-making, and concluded that the most plausible incremental cost-effectiveness ratio (ICER) for sacubitril valsartan compared with ACE inhibitors to be £29,500 per quality-adjusted life year (QALY) gained. The most plausible ICER for sacubitril valsartan compared with ARBs in people who cannot have	4.17 4.18

an ACE inhibitor was £30,100 per QALY gained. The Committee considered that, given the innovative nature of sacubitril valsartan, the most plausible ICERs of £29,500 and £30,100 per QALY gained for sacubitril valsartan compared with ACE inhibitors and ARBs (for people who cannot have an ACE inhibitor) respectively, represented a cost-effective use of NHS resources. It concluded that, given the issues of generalisability of the PARADIGM-HF trial to clinical practice in England regarding factors such as age, cardiac device use, and treatment tolerability, it was important that the recommendations closely reflected the population in the trial.		
Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee heard from the clinical experts that people with chronic heart failure have a poor quality of life. The Committee recognised the impact of chronic heart failure on quality of life and concluded that there were potential treatment benefits with sacubitril valsartan for people who are covered by the marketing authorisation.	4.1
The technology		

Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee concluded that, for the overall population included in the PARADIGM-HF trial, sacubitril valsartan was statistically significantly more clinically effective than enalapril at improving both overall mortality and cardiovascular mortality and reducing hospitalisations. The Committee concluded that sacubitril valsartan was innovative and that it offered a small step-change in the management of this condition.	4.4 4.19
What is the position of the treatment in the pathway of care for the condition?	The Committee concluded that sacubitril valsartan should only be offered to patients who are already taking a stable dose of ACE inhibitors or ARBs.	4.2
Adverse reactions	The Committee concluded that sacubitril valsartan had a manageable adverse event profile in the population specified in the marketing authorisation.	4.7
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The pivotal clinical evidence presented in the company's submission was derived from the PARADIGM-HF trial which was a randomised, double-blind, controlled, phase III trial comparing sacubitril valsartan with enalapril. The Committee considered the PARADIGM-HF trial was a good quality trial and that the	4.4

	relevant clinical outcomes of mortality and hospital admission were assessed.	
Relevance to general clinical practice in the NHS	The Committee noted that compared with general clinical practice in the NHS, people in the PARADIGM-HF trial were younger, included a higher proportion of men, were less likely be using cardiac devices, and had greater tolerability to the dose of valsartan (in sacubitril valsartan; equivalent to 160 mg of valsartan given alone). The Committee was persuaded that the issue of generalisability was similar across all trials in this condition, and it concluded that, despite the differences between the trial and the trial eligible population in England, the results of the PARADIGM-HF trial were relevant to routine clinical practice.	4.3
Uncertainties generated by the evidence	The Committee acknowledged there was some uncertainty because of the lack of generalisability of the PARADIGM-HF trial results (as a result of the younger age, lower cardiac device use, and greater tolerability to treatments), but it agreed that this issue was similar across all trials in this condition, and it concluded that, despite the differences between the trial and the trial eligible population in England, the results of the PARADIGM-HF trial were relevant to established clinical practice in England.	4.3

Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee noted that in the total trial population, the composite primary end point (death from cardiovascular causes or a first hospitalisation for worsening heart failure) significantly favoured sacubitril valsartan compared with enalapril (hazard ratio [HR] 0.80; 95% confidence interval [CI] 0.73 to 0.87, p<0.001). The treatment effect in the Western Europe group also favoured sacubitril valsartan, although this was not statistically significant (HR 0.89, 95% CI 0.74 to 1.07). The Committee concluded the lack of statistical significance associated with this subgroup would not factor in its decision-making. Results of the network meta-analysis demonstrated that sacubitril valsartan was superior to ARBs with regards to all-cause and cardiovascular mortality and broadly equivalent with regards to all-cause hospitalisation outcomes.	4.4 4.5 4.6
Evidence for cost effectiveness		
Availability and nature of evidence	The Committee considered the company's economic model and the critique of the model by the ERG to inform its discussions. It concluded that the company's model was sufficiently robust for assessing the cost effectiveness of sacubitril valsartan.	4.11

Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee agreed that there was some uncertainty as to whether the ERG's additional analysis in 75-year olds was fully reflective of the true cost-effectiveness of sacubitril valsartan in an older population.	4.12
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The company used a linear mixed regression model based on EQ-5D trial data from PARADIGM-HF to predict utility scores. The Committee considered the issues raised by the ERG, in particular that the trial (and consequently the model outcomes) could potentially be biased in favour of the sacubitril valsartan group if, for example, patients in this group had a better quality of life at baseline, and this healthier state may be carried through to the trial and result in better outcomes. The Committee agreed that the ERG's exploratory analyses in which it used a simplified approach to estimating quality of life and used a baseline utility from Berg et al. were both more appropriate than the company's base case for the purposes of decision-making. No additional significant and substantial health-related benefits were identified that were not included in the economic model.	4.14

What are the key drivers of cost effectiveness?	The greatest effects on the ICER for both the primary and secondary base case analyses came from the treatment effect of sacubitril valsartan on mortality, the baseline risk of mortality, and age (as a result of its impact on expected survival).	3.30
Most likely cost-effectiveness estimate (given as an ICER)	The Committee concluded that the most plausible ICER for sacubitril valsartan compared with ACE inhibitors was £29,500 per QALY gained. The most plausible ICER for sacubitril valsartan compared with ARBs in people who cannot have an ACE inhibitor was £30,100 per QALY gained.	4.17 4.18
Additional factors taken into account		
Patient access schemes (PPRS)	There is no patient access scheme	
End-of-life considerations	Not applicable	

Equalities considerations and social value judgements	The Committee discussed comments received during consultation that noted the higher rates of angio-oedema in those of African family origin having ACE inhibitors. Bearing in mind that the Committee had recommended sacubitril valsartan, it concluded that there was no unfairness or unlawful discrimination and no need to alter or add to its recommendations.	4.20

5 Implementation

5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has heart failure with reduced ejection fraction and the doctor responsible for their care thinks that

sacubitril valsartan is the right treatment, it should be available for use, in line with NICE's recommendations.

5.4 NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the NICE website.

- Chronic heart failure: Management of chronic heart failure in adults in primary and secondary care. NICE clinical guideline 108 (2010).
- Ivabradine for treating chronic heart failure. NICE technology appraisal guidance no. 267 (2012).
- Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure. NICE technology appraisal guidance no. 314 (2014).

- Insertion and use of implantable pulmonary artery pressure monitors in chronic heart failure. NICE interventional procedure guidance 463 (2013).

7 Proposed date for review of guidance

7.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Professor Andrew Stevens
Chair, Appraisal Committee
December 2015

8 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Andrew Stevens
Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Professor Eugene Milne
Vice Chair of Appraisal Committee C, Director of Public Health, City of Newcastle upon Tyne

Mr David Chandler
Lay member

Gail Coster
Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

Professor Peter Crome

Honorary Professor, Dept of Primary Care and Population Health, University College London

Dr Nigel Langford

Consultant in Clinical Pharmacology and Therapeutics and Acute Physician, Leicester Royal Infirmary

Dr Patrick McKiernan

Consultant Pediatrician, Birmingham Children's Hospital

Dr Andrea Manca

Health Economist and Senior Research Fellow, University of York

Dr Iain Miller

Founder & CEO, Health Strategies Group

Dr Anna O'Neill

Deputy Head of Nursing & Healthcare School / Senior Clinical University Teacher, University of Glasgow

Dr Claire Rothery

Research Fellow in Health Economics, University of York

Professor Peter Selby

Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Professor Matt Stevenson

Technical Director, School of Health and Related Research, University of Sheffield

Professor Robert Walton

Clinical Professor of Primary Medical Care, Barts and The London School of Medicine & Dentistry

Dr Judith Wardle

Lay member

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Chris Chesters

Technical Lead

Nicola Hay

Technical Adviser

Lori Farrar/Stephanie Yates

Project Manager

9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by BMJ Group:

- Edwards SJ, Crawford F, Osei-Assibey G Bacelar M, Berardi A, Salih F. Sacubitril valsartan for treating chronic heart failure: A Single Technology Appraisal. BMJ-TAG, 2015.

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to make written submissions. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- Novartis

II. Professional/expert and patient/carer groups:

- Pumping Marvellous Foundation
- South Asian Health Foundation
- British Society for Heart Failure
- Royal College of Pathologists
- Royal College of Physicians

III. Other consultees:

- Department of Health
- NHS Doncaster CCG
- NHS England
- NHS Surrey Heath CCG
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Servier

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on Sacubitril valsartan for treating heart failure with reduced ejection fractionby attending the initial Committee discussion and

providing a written statement to the Committee. They are invited to comment on the ACD.

- Dr Simon Williams, Consultant Cardiologist, nominated by Novartis – clinical expert
- Dr Lisa Anderson, Heart Failure Consultant, nominated by The British Society for Heart Failure – clinical expert
- Nick Hartshorne-Evans, nominated by Pumping Marvellous Foundation – patient expert
- Emma Taylor, nominated by Pumping Marvellous Foundation – patient expert

E. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Novartis Pharmaceuticals