NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

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

- with New York Heart Association (NYHA) class 2 to 4 symptoms and
- with a left ventricular ejection fraction of 35% or less and
- who are already taking a stable dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor-blockers (ARBs).

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 performed by the most appropriate team member as defined in NICE's guideline on chronic heart failure in adults: diagnosis and management.

1.3 This guidance is not intended to affect the position of patients whose treatment with sacubitril valsartan was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published 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'. Before the marketing authorisation was granted, sacubitril valsartan was available in the NHS through the early access to medicines scheme. 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 one 49/51 mg tablet, twice daily (each tablet contains 48.6 mg sacubitril and 51.4 mg valsartan). The dose should be doubled at 2 to 4 weeks to the target dose of one 97/103 mg tablet (97.2 mg sacubitril and 102.8 mg valsartan) 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; MIMS, April 2016):

- 24/26 mg (containing 24.3 mg sacubitril and 25.7 mg valsartan), 28 pack: £45.78
- 49/51 mg (containing 48.6 mg sacubitril and 51.4 mg valsartan), 28 pack: £45.78
- 49/51 mg (containing 48.6 mg sacubitril and 51.4 mg valsartan), 56 pack: £91.56
- 97/103 mg (containing 97.2 mg sacubitril and 102.8 mg valsartan), 56 pack: £91.56.

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

3 Evidence

The appraisal committee considered evidence submitted by Novartis and a review of this submission by the evidence review group (ERG).

Clinical effectiveness

3.1 The pivotal clinical evidence presented in the company's submission was taken from the PARADIGM-HF trial, which compared sacubitril valsartan with enalapril (an angiotensin-converting enzyme [ACE] inhibitor). The company also did 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 (a multicentre, randomised, double-blind, parallel group, phase 2 study in clinically stable outpatients or hospitalised patients), which evaluated the safety and tolerability of sacubitril valsartan at increasing doses.

3.2 PARADIGM-HF was a randomised, double-blind, controlled, phase 3 trial comparing sacubitril valsartan (n=4,187) with enalapril (n=4,212). 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 2 to 4 – with left ventricular ejection fraction (LVEF) of 35% or lower. The company chose enalapril as a comparator in the trial 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 (around 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 2 to 4, some people had an improvement in their NYHA class between screening and randomisation, so nearly 5% of randomised patients were NYHA class 1. 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. Raised plasma B-type natriuretic peptide (BNP) level of at least 150 pg per ml (or N-terminal pro-brain natriuretic peptide [NT-proBNP] of at least 600 pg per ml) at screening was also an entry criterion. If patients had been hospitalised for heart failure in the past 12 months, then a slightly lower cut-off for BNP level (100 pg per ml) or an NT-proBNP level (400 pg per ml) was accepted.

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% more 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=8,399). 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 compared with enalapril showed a significantly reduced risk for 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 to 0.95, p<0.0008). The KCCQ patient scores were reduced for both sacubitril valsartan and enalapril, but 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 a number of 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 in people aged 75 years and older (HR 0.86, 95% CI 0.72 to 1.04), and people with NYHA class 3 or 4 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=1,867), 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 Heran et al. (2012) in a Cochrane review, which assessed ACE inhibitors against ARBs with regard to morbidity and mortality irrespective of concomitant treatment with standard care therapies.

3.13 The company's 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 justify 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 cited the Cochrane review by Heran et al. (2012) to support 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 regard to all-cause and cardiovascular mortality and broadly equivalent with regard to all-cause hospitalisation outcomes
- sacubitril valsartan was superior to ACE inhibitors with regard to all-cause and cardiovascular mortality and superior with regard 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 the technology appraisal guidance on ivabradine for treating chronic heart failure. In the company's 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 (8,399). Actual model outcomes were obtained by averaging across the 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's 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 how it affects patients' quality of life. Adverse events in the trial that were 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 quality-adjusted life year (QALY) gained (representing incremental costs of £7,514 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 the maximum acceptable ICERs of £20,000 and £30,000 per QALY

gained 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 effect 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 £8,513 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 the maximum acceptable ICERs of £20,000 and £30,000 per QALY gained 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).

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 younger 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 comorbidities 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 affected 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 because 70% of patients had been diagnosed for more than 1 year, and almost all patients were already having either ACE inhibitors or ARBs before entry in to the trial.
- 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: diagnosis and management that 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 effect of continuing these patients on ACE inhibitors was likely to misrepresent what would happen in patients who have not previously had ACE inhibitors or ARBs. 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 effect on the observed relative effectiveness of sacubitril valsartan, which may be overestimated in the trial population when compared with patients who have not previously had ACE inhibitors or ARBs.

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 because of the clinical heterogeneity in the trials underpinning the network.

3.40 The ERG discussed 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 stated that the company did not provide a clear justification for choosing a patient-level approach when modelling clinical effectiveness.

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: diagnosis and 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 affects 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. The ERG also noted 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 effect 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 effect 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-naive 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 affected 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 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. Sacubitril valsartan's effect 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 effect 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

Results per patient	Sacubitril + SoC	Enalapril + SoC	Incremental value
Company's base case with ERG corrections QALYs	5.40	4.82	0.58
Company's base case with ERG corrections ICER			**£15,026**
Mean age at baseline of 75 years Total costs (£)	£19,498	£12,562	£6,936
Mean age at baseline of 75 years QALYs	4.43	3.99	0.44
Mean age at baseline of 75 years ICER (compared with base case)	–	–	**£15,843**
Mean age at baseline of 75 years 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
Change in baseline utility to reflect Berg et al utility (0.72) QALYs	5.11	4.55	0.55
Change in baseline utility to reflect Berg et al utility (0.72) ICER (compared with base case)	–	–	**£15,407**
Change in baseline utility to reflect Berg et al utility (0.72) ICER with all changes incorporated	–	–	**£16,190**
Change in QoL modelling approach Total costs (£)	£22,961	£14,308	£8,653
Change in QoL modelling approach QALYs	5.30	4.80	0.50

Results per patient	Sacubitril + SoC	Enalapril + SoC	Incremental value
Change in QoL modelling approach ICER (compared with base case)	–	–	**£17,413**
Change in QoL modelling approach ICER with all changes incorporated	–	–	**£19,697**
Total costs (£)	£23,085	£14,430	£8,655
QALYs	5.40	4.82	0.58
Change in pharmaceutical costs to reflect drug target doses ICER (compared with base case)	–	–	**£15,030**
Change in pharmaceutical costs to reflect drug target doses 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
Change in pharmaceutical costs to reflect the cost of ramipril QALYs	5.40	4.82	0.58
Change in pharmaceutical costs to reflect the cost of ramipril ICER (compared with base case)	–	–	**£15,115**
Change in pharmaceutical costs to reflect the cost of ramipril ICER with all changes incorporated	–	–	**£19,843**
Western Europe subgroup Total costs (£)	£24,182	£17,341	£6,841
Western Europe subgroup QALYs	4.86	4.52	0.33
Western Europe subgroup 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).

Company's new evidence in response to consultation

3.62 In response to the consultation, the company requested permission to submit new evidence, which was granted by NICE. The new evidence was to support the clinical effectiveness and safety of sacubitril valsartan in people not included in the draft recommendations, specifically:

- people with NYHA class 4 symptoms (see section 3.63)
- people who have not previously had ACE inhibitors or ARBs (see sections 3.64 to 3.67)
- people with LVEF more than 35% (see section 3.68).

3.63 The company presented effectiveness data for a post-hoc subgroup of patients in the PARADIGM-HF trial with NYHA class 4 symptoms at randomisation (n=60). The data showed that the primary end point was observed in 33.30% (10 out of 33) of patients having sacubitril valsartan compared with 40.74% (11 out of 27) of patients having enalapril (HR 0.71, 95% CI 0.30 to 1.69). Lower rates of cardiovascular deaths were also seen in this subgroup for patients having sacubitril valsartan (18.8%, 6 out of out of 33 patients) than in those having enalapril (22.22%, 6 out of 27 patients; HR 0.87, 95% CI 0.28 to 2.73). The company did not present data for the other component of the primary outcome

for this subgroup (that is, first hospitalisation for worsening heart failure). The company also stated that 323 patients had NYHA class 4 symptoms during the double-blind phase of the trial but did not present any further information for these patients. The company also presented safety data for this subgroup that showed that for people having sacubitril valsartan, the proportions of patients with at least 1 adverse event (72.3%), hypotension (9.09%), renal impairment (6.06%) and hyperkalaemia (15.5%) were comparable to those in people with NYHA class 2 (82.11%, 17.39%, 9.79% and 11.69% respectively) and NYHA class 3 (78.53%, 18.71%, 11.04% and 12.07% respectively).

3.64 To demonstrate the clinical efficacy of sacubitril valsartan in people who have not previously had ACE inhibitors or ARBs, the company suggested that a subgroup of the PARADIGM-HF trial comprising people who had been diagnosed less than 3 months before entering the trial could be considered a proxy. The company stated that for this subgroup analysis, the p value of statistical interaction was 0.2677. From this statistically non-significant interaction, the company inferred that the treatment benefit of sacubitril valsartan over ACE inhibitors was independent of time since diagnosis. The company interpreted from this that the treatment benefit of sacubitril valsartan over ACE inhibitors would also be seen in people who have not previously had ACE inhibitors or ARBs.

3.65 The company stated that in the PARADIGM-HF trial, the treatment benefit of sacubitril valsartan compared with enalapril for the primary composite end point and heart failure hospitalisations was evident in the first 30 days after randomisation. To support this, the company presented 2 graphs showing Kaplan–Meier estimates for the first 30 days after randomisation. These graphs demonstrated a decreased hazard for the first hospitalisation for heart failure (HR 0.60, 95% CI 0.38 to 0.94, p=0.027) and 'sudden death' (HR 0.80, 95% CI 0.68 to 0.94, p=0.08) in people having sacubitril valsartan within the first 30 days. The company did not define sudden death, but stated that it was the most common cause of death in the trial and attributed it to 36.23% of total deaths. The company did not present corresponding graphs and data for the primary end point or cardiovascular death.

3.66 To support the safety and tolerability of sacubitril valsartan in people who have not previously had ACE inhibitors or ARBs, the company stated that in the TITRATION study most of these patients were able to achieve and maintain the

target dose of sacubitril valsartan.

3.67 The company also presented safety data in people who have not previously had ACE inhibitors or ARBs from the studies evaluating sacubitril valsartan for treating hypertension (a different indication than chronic heart failure). The company presented the percentages of patients with at least 1 adverse event, at least 1 serious adverse event and with adverse events leading to discontinuation. The data compared the safety profile of sacubitril valsartan with placebo, olmesartan, amlodipine and valsartan only in people who have not previously had ACE inhibitors or ARBs. The company did not present corresponding data for people who had previously had ACE inhibitors or ARBs. However, it concluded that these data demonstrated a comparable safety profile for sacubitril valsartan independent of previously having ACE inhibitors or ARBs.

3.68 To support the effectiveness of sacubitril valsartan in people with LVEF of more than 35%, the company presented 2 post-hoc analyses of the PARADIGM-HF trial for the subgroups defined by ejection fraction at baseline. In the first analysis, the company defined the subgroups on the basis of LVEF at screening (less than 28%, 28% to 33%, and more than 33%). The company presented a forest plot that showed that for the primary end point, the point estimates in all 3 subgroups were comparable and that the p value for statistical interaction among subgroups was 0.9720. In the second analysis, the company defined 5 subcategories on the basis of LVEF at screening: 15% or less, 16% to 20%, 21% to 25%, 26% to 30%, 31% to 35%, and more than 35%. The company reported that there were no significant subgroup interactions for either the primary end point (p=0.9377) or cardiovascular death (p=0.3367), but did not present point estimates in these subgroups for either outcome.

3.69 The company commented on the ERG's exploratory analyses, highlighting that using the hazard ratio from a subgroup (Western Europe) instead of overall population (see sections 3.56 and 3.59) had no statistical basis because there was no subgroup-treatment effect interaction (p=0.373). The company also noted that the Western Europe subgroup was not powered to detect statistically significant differences in the primary end point. The company also commented that in the PARADIGM-HF trial, point estimates for all subgroup analyses suggested a benefit in the sacubitril valsartan group and different treatment effect in subgroups should be interpreted with caution. Applying clinical

effectiveness from the overall population on the ERG's preferred scenario, the company calculated an ICER of £19,843 per QALY gained for sacubitril valsartan compared with ACE inhibitors.

3.70 The company also commented that the ERG's alternative approach for modelling quality of life did not take into account the utility benefit of sacubitril valsartan (0.011), which was derived from the difference in the EQ-5D scores between the 2 treatment groups in the trial after controlling for the effects of hospitalisations and adverse events. The company did not agree with the ERG's rationale that there may have been a statistically significant difference in patients' EQ-5D scores at baseline, which may have biased the EQ-5D outcomes in favour of sacubitril valsartan; the EQ-5D analysis was based on a repeated measures ANCOVA model that controls for random differences or imbalance in baseline scores. The company justified the assumption of utility benefit with sacubitril valsartan, noting that in PARADIGM-HF more people having sacubitril valsartan than those having enalapril had symptomatic benefit, as evidenced by improvement in KCCQ scores and NYHA class. Applying a utility gain of 0.011 with sacubitril valsartan over all other ERG-preferred assumptions, the company calculated an ICER of £25,607 per QALY gained for sacubitril valsartan compared with ACE inhibitors.

ERG's critique of company's new evidence

3.71 The ERG commented that the new evidence for sacubitril valsartan's effectiveness and safety in people with NYHA class 4 heart failure at baseline (see section 3.63) was based on a small sample size (n=60) compared with the overall number of patients in PARADIGM-HF: the full analysis set for the primary end point comprised 8,399 patients and 5,931 patients in the safety analysis who had a NYHA classification at baseline. The ERG commented that the lack of statistically significant difference in the treatment effect between sacubitril valsartan and enalapril in the NYHA class 4 subgroup would increase the uncertainty in estimating the cost effectiveness of sacubitril valsartan in these patients. The ERG also noted that the company did not clarify why it chose only 3 adverse events (hypotension, renal impairment and hyperkalaemia) to compare the safety of sacubitril valsartan with that of enalapril in this subgroup.

3.72 The ERG noted that the company did not provide data to support its assumption that sacubitril valsartan would be as effective in patients who have not previously had ACE inhibitors or ARBs as those who have. The ERG queried the relevance of new evidence presented by the company (see sections 3.64 to 3.67) for people with chronic heart failure who have not previously had ACE inhibitors or ARBs.

3.73 The ERG acknowledged that the post-hoc analyses for subgroups based on LVEF at baseline (see section 3.68) supported the clinical benefit of sacubitril valsartan over enalapril across different subgroups. However, it did not consider that these analyses provided enough evidence to assume an equal effect in people with LVEF more than 35% and in people with LVEF of 35% or less. For the second analysis that considered 5 subgroups, the ERG commented that the company did not provide details of the analysis such as the number of patients and the estimated effects in each subgroup.

4 Committee discussion

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 included in 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 affect everyday tasks, with comorbidities increasing the burden 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 how chronic heart failure affects quality of life and concluded that there were treatment benefits with sacubitril valsartan for people who are covered by the marketing authorisation.

Clinical effectiveness

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 both patients who have and have not previously had ACE inhibitors or angiotensin II receptor-blockers (ARBs). The committee heard from the clinical experts that clinical practice is broadly in line with NICE's guideline on chronic heart failure in adults: diagnosis and 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 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 many of patients with newly diagnosed heart failure may already be taking an ACE inhibitor for other conditions (for example hypertension). The committee heard from one of the clinical experts that people who are newly diagnosed with chronic heart failure but are already taking an ACE inhibitor or ARB would likely be offered sacubitril valsartan. However, the clinical expert explained that they would be reluctant to give sacubitril valsartan to people who had not previously had ACE inhibitors or ARBs because of the lack of evidence for clinical effectiveness and safety of sacubitril valsartan in this population. They also noted that in allowing the marketing authorisation for the drug to extend to patients who have not previously had ACE inhibitors or ARBs, the European Medicines Agency had recommended a lower starting dose. The committee agreed there was a lack of evidence in people who have not previously had 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 discussed comments it had received during consultation about the lack of clinical efficacy data from PARADIGM-HF in people with chronic heart failure who have not previously had ACE inhibitors or ARBs. It noted that the a priori subgroup analyses of the PARADIGM-HF trial, based on the time since diagnosis (less than 1 year, 1 to 5 years, and more than 5 years), and a post-subgroup analysis for patients diagnosed less than 3 months previously did not show any statistically significant interaction between the subgroup demonstrating that the treatment effect would not vary depending up on the time since diagnosis (see section 3.64). However, the committee understood that the PARADIGM-HF trial was designed to evaluate the efficacy of sacubitril valsartan in people who were already taking an optimised dose of ACE inhibitors or ARBs. It was not persuaded that the analysis showing early onset of treatment effect in the PARADIGM-HF trial could be used as a proxy to demonstrate the effect in patients who have not previously had ACE inhibitors or ARBs (see section 3.65). The committee agreed that all these analyses included people who were already having optimum treatment for heart failure, and that the evidence of effectiveness within the first 30 days or in people who were recently diagnosed could not be used as a substitute for the lack of evidence in people who have not previously had ACE inhibitors or ARBs. The committee also agreed that in the absence of any trial data for this

population, sacubitril valsartan's effectiveness remains uncertain. The committee concluded that sacubitril valsartan should only be offered, in place of ACE inhibitors or ARBs, to patients who are symptomatic despite already taking a stable dose of ACE inhibitors or ARBs.

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 committee noted the consultation comment that baseline age in the PARADIGM-HF trial was similar to that seen in other trials that established the effectiveness of ACE inhibitors, beta blockers, aldesterone antagonists, implantable cardiac devices and ivabradine in chronic heart failure. 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 its dose-dependent nature. 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 New York Heart Failure (NYHA) class 3 or 4 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 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 agreed 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 based on race, age and cardiac device use at baseline for the Western Europe subgroup. Baseline characteristics of the Western Europe subgroup were designated academic in confidence by the company and therefore not reported here. The committee was aware that the treatment effect was not statistically significantly different compared with enalapril in this subgroup. The committee also noted the difference in the aetiology of chronic heart failure (ischaemic and non-ischaemic), baseline risk for the mortality and the clinical management of heart failure between the different regions from which the population in the trial was recruited, and agreed that patients in the Western Europe subgroup were more comparable to patients in clinical practice in England than the total trial population. It concluded that the Western Europe subgroup was the most representative of clinical practice in England, and therefore the magnitude of effect for sacubitril valsartan generalisable to clinical practice in England will be closer to the results in the Western Europe.

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 regard to all-cause and cardiovascular mortality and broadly equivalent with regard 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 these 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 because people in clinical practice are generally older 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 in the trial because of possible hypotension-related adverse events. The committee noted the consultation comment from one of the clinical experts advocating a judicious use of sacubitril valsartan in line with the inclusion criteria of PARADIGM-HF trial. The main concern raised by the clinical expert was the lack of long-term data on its effect on cognitive function and a higher incidence of angioedema in people of African family origin. The committee heard from the company that these safety aspects are covered in the risk management plan agreed by the European Medicines Agency and the company. 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 at what left ventricular ejection fraction level sacubitril valsartan could be considered an appropriate treatment for chronic heart failure. It was aware that the 'reduced ejection fraction' was not specified in the marketing authorisation and that the left ventricular ejection fraction entry criterion for the PARADIGM-HF trial was changed from 40% or less to 35% or less. The committee heard from the company that improvement in clinical care, attributed to increased use of aldosterone antagonists, had reduced the baseline risk for cardiovascular mortality and hospitalisation. Therefore, the cut-off was lowered from 40% to 35% in the trial to offset this anticipated decrease in the

event rates for the outcomes. The committee noted that subgroup analyses based on baseline left ventricular ejection fraction showed no statistically significant interaction in the relative treatment effect of sacubitril valsartan over enalapril among these subgroups. However, given that most of the patients in the trial had left ventricular ejection fraction of 35% or less, the committee agreed that there was weaker evidence of clinical effectiveness in people with left ventricular ejection fraction of more than 35% to 40%. Furthermore, the lower event rate for people with the higher left ventricular ejection fraction of more than 35% to 40%, acknowledged by the company, meant less potential to benefit from sacubitril valsartan and implied a smaller incremental QALY gain and therefore poorer cost effectiveness (see section 4.20). The committee discussed how the left ventricular ejection fraction level will be determined in clinical practice and whether the necessary tests will be readily available to people who may benefit from sacubitril valsartan. It understood that left ventricular ejection fraction level is usually established with an echocardiogram and additional tests will not necessarily be needed before starting treatment with sacubitril valsartan. The committee noted the consultation comments that there are variations with respect to the reporting of echocardiogram assessments of left ventricular function, but noted that a cut-off of 35% or less has been used in other NICE guidance in this disease area and agreed that this was accepted as an indicator of severe left ventricular dysfunction in clinical practice. The committee concluded that sacubitril valsartan should only be given to people with a left ventricular ejection fraction of 35% or less, normally shown on an echocardiogram.

4.9 The committee explored in which NYHA classes sacubitril valsartan could be considered an appropriate treatment option for 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 2 to 4, but that most patients in the trial had NYHA class 2 to 3 (0.7% [60 patients] had NYHA class 4 heart failure). The committee agreed that the representation of patients with NYHA class 4 was limited and that the effectiveness of sacubitril valsartan was imprecise (associated with a wide confidence interval) as expected because of the small number of patients in this subgroup. The committee noted the consultation comments that it would be clinically counterintuitive not to recommend sacubitril valsartan in this patient group when it was recommended in patients with milder

symptoms of chronic heart failure (NYHA classes 2 and 3). The committee noted the limited adverse events data presented by the company comparing patients with NYHA class 2, 3 and 4 symptoms at baseline (see section 3.63) and was reassured by the comparable safety profile of sacubitril valsartan in these groups. The committee understood that it is difficult to recruit severely symptomatic patients, as evident by the low number of NYHA class 4 patients in PARADIGM-HF and other trials in chronic heart failure. Overall, the committee was persuaded that sacubitril valsartan was an appropriate treatment option in people with NYHA class 2, 3 or 4 chronic heart failure.

4.10 The committee explored whether a high plasma B-type natriuretic peptide (BNP) level was necessary for sacubitril valsartan to be considered an appropriate treatment option for chronic heart failure. The committee considered the inclusion criteria for the PARADIGM-HF trial, noting that they specified a high BNP level of at least 150 pg per ml (or an N-terminal pro-B-type natriuretic peptide [NTproBNP] level of at least 600 pg per ml). It also noted that the inclusion criteria specified that if the patient had been hospitalised within the last 12 months because of heart failure, a slightly lower cut-off BNP (100 pg per ml, or NTproBNP 400 pg per ml) was accepted. The committee understood that BNP is a marker for heart failure, used in the diagnosis of chronic heart failure as well as monitoring the response to treatment. However, it is not specific to heart failure and in the acute setting is mostly used to rule out the presence of acute heart failure in the presence of symptoms like breathlessness. The committee noted that because of its mechanism of action as a neprilysin inhibitor, sacubitril valsartan will affect BNP level, and also that the summary of product characteristics does not recommend BNP as a suitable biomarker of heart failure in patients having sacubitril valsartan. The committee considered a consultation comment that compared the mean baseline BNP level in the trial population (225 pg per ml) with the mean value in stable patients as reported in the literature (93 pg per ml), along with commentary suggesting that sacubitril valsartan may not be as effective in patients with lower BNP. The committee heard from the company that the mean BNP level for people in secondary care reported in Hull Heart Failure Registry was comparable to the baseline value seen in the PARADIGM-HF trial. The committee understood that high BNP level in patients with chronic failure is an indicator of ventricular dysfunction and although there is no direct correlation between reduced left ventricular ejection fraction and high BNP level, they tend to coexist. The committee noted that

NICE's guideline on chronic heart failure in adults: diagnosis and management makes specific recommendations about using BNP or NTproBNP in diagnosing and managing chronic heart failure. It concluded that BNP need not be further specified when considering starting a patient on sacubitril valsartan in addition to reduced left ventricular ejection fraction (see section 4.8).

4.11 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 committee noted that NICE's guideline on chronic heart failure in adults: diagnosis and 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 had not previously had 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. The committee acknowledged the consultation comments highlighting the lack of available GPs with a special interest in heart failure and heart failure specialist nurses in the community. It further noted comments suggesting that the dose monitoring and titration could be done by GPs who may not have a special interest in heart failure. The committee noted that NICE's guideline on chronic heart failure in adults: diagnosis and management recommended that the multidisciplinary heart failure team should decide regarding who is the most appropriate team member to address a particular clinical problem. Therefore, the committee concluded that dose titration and monitoring should then be done by a heart failure specialist or in primary care by the most appropriate team member, as specified in NICE's guideline on chronic heart failure in adults: diagnosis and management.

Cost effectiveness

4.12 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's 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 (see section 3.43). 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 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.

4.13 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 in order to generalise the model results. It understood that the model was accurate in replicating the trial data, but that there were issues of face validity (such as 21-year olds having the same life expectancy as 87-year olds; 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, and further recalled its concern about the sacubitril valsartan dose used in the trial. Nevertheless, 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.

4.14 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 regarding the generalisability of clinical effectiveness 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 closer to this subgroup more appropriate for the cost-effectiveness analyses comparing sacubitril valsartan with ACE inhibitors and ARBs.

4.15 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 discussed whether using a utility benefit of 0.011 in patients having sacubitril valsartan over and above those generated by the difference in these outcomes was reasonable. 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 3.56). 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 effect of reduced hospitalisation. It also noted that the ERG had not included the absolute utility increment (0.011) with sacubitril valsartan because of concerns regarding the difference in the baseline EQ-5D values between the 2 arms of the PARADIGM-HF trial (see section 3.55). The committee heard from the company that it had adjusted for any imbalance in the baseline EQ-5D values using an analysis of covariance (ANCOVA). The committee agreed that there may have been other benefits due to symptomatic improvement of the chronic condition that may not have been captured in the ERG's analyses, and so was persuaded that some additional utility benefit for patients having sacubitril valsartan – as suggested by the company – could be accepted for the purposes of decision-making.

4.16 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 effect on the cost-effectiveness results, but the committee agreed that the use of ramipril costs rather than enalapril costs more appropriately reflected clinical practice in England.

4.17 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 cost-effectiveness results, but concluded that a consistent approach to the use of drug doses was more appropriate to inform its decision-making.

4.18 The committee considered the incremental cost-effectiveness ratios (ICERs) presented by the company for sacubitril valsartan compared with ACE inhibitors, as well as the 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 costs £7,514, incremental QALYs 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 conclusion that the outcome expected to be seen in clinical practice in England would be closer to the results for the Western European group than the overall trial population (see section 4.5). The committee agreed that it would accept the central estimate of effect for the Western European subgroup. The committee recalled its conclusion that the company's approach to modelling utility benefit with sacubitril valsartan was plausible (see section 4.15) and noted that during consultation the company, applying all of the ERG's assumptions with the exception of its approach to modelling utility values, estimated an ICER of about £26,000 per QALY gained for sacubitril valsartan compared with ACE inhibitors (see section 3.70).

4.19 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, resulting in an ICER of £30,100 per QALY gained. The committee did not have an exact figure for the ICER underpinning its preferred assumptions, which included all assumptions in the ERG's preferred scenario except the additional utility benefit with sacubitril valsartan. However, from the effect of these assumptions on the ICER for sacubitril valsartan compared with ACE inhibitors (see section 4.18), the committee concluded that the most plausible ICER for sacubitril valsartan

compared with ARBs in people who cannot have an ACE inhibitor would be less than £30,000 per QALY gained.

4.20 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 processes 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 an Early Access to Medicines Scheme positive opinion 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 for sacubitril valsartan – between £26,000 and £30,000 per QALY gained – could be considered to represent a cost-effective use of NHS resources. However, it acknowledged that there were considerable uncertainties in the data including: non-significant results in the Western European subgroup; a high sacubitril valsartan dose that may not be replicable in clinical practice; limited representation of patients with NYHA class 4 symptoms; the weaker evidence (as well as lower event rate and therefore less potential to benefit) for patients with a left ventricular ejection fraction of over 35%; and the absence of direct evidence for patients who have not previously had ACE inhibitors or ARBs. These latter 2 groups (people with a left ventricular ejection fraction of over 35% and people who have not previously had ACE inhibitors or ARBs) could not be assumed to have the same cost-effectiveness level as that modelled for the core trial population. The committee therefore considered that its recommendations should closely reflect the core population in the PARADIGM-HF trial and agreed that people with NYHA class 4 should not be excluded from the recommendations.

The committee concluded that sacubitril valsartan is a cost-effective use of NHS resources for treating chronic heart failure with reduced ejection fraction, only in people with NYHA class 2 to 4 chronic heart failure, who are already taking a stable dose of ACE inhibitors or ARBs and have a left ventricular ejection fraction of 35% or less.

4.21 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%). Mindful of its recommendations for sacubitril valsartan, the committee concluded that there was no unfairness or unlawful discrimination and no need to alter or add to its recommendations.

4.22 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.

5 Implementation

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

5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

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 healthcare professional responsible for their care thinks that sacubitril valsartan is the right treatment, it should be available for use, in line with NICE's recommendations.

6 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

Professor Kathryn Abel
Institute of Brain and Behaviour Mental Health, University of Manchester

Dr Ian Bernstein
General Practitioner and Musculoskeletal Physician, NHS Ealing CCG

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

Professor Rachel A Elliott
Lord Trent Professor of Medicines and Health, University of Nottingham

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 Paul Miller
Director, Payer Evidence, Astrazeneca UK Ltd

Dr Anna O'Neill
Deputy Head of Nursing & Healthcare School and Senior Clinical University Teacher, University of Glasgow

Professor Andrew Renehan
Professor of Cancer Studies and Surgery, The Christie NHS Foundation Trust

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

Dr Paul Tappenden
Reader in Health Economic Modelling, 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 and Anwar Jilani
Technical Leads

Nicola Hay
Technical Adviser

Lori Farrar and Stephanie Yates
Project Managers

7 Sources of evidence considered by the Committee

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.

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). Companies were also invited to make written submissions. Professional or expert and patient or carer groups, and other consultees, had the opportunity to make written submissions. Companies, professional or expert and patient or carer groups, and other consultees, also have the opportunity to appeal against the final appraisal determination.

Company:

- Novartis

Professional or expert and patient or carer groups:

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

Other consultees:

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

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

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 fraction by 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

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

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