NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Empagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using empagliflozin in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

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

Issue date: February 2023

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

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using empagliflozin in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 1 March 2023
- Second evaluation committee meeting: 12 April 2023
- Details of membership of the evaluation committee are given in section 4.

1 Recommendations

1.1 Empagliflozin is not recommended, within its marketing authorisation, for treating symptomatic chronic heart failure with preserved or mildly reduced ejection fraction in adults.

1.2 This recommendation is not intended to affect treatment with empagliflozin that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Current standard care for heart failure with preserved or mildly reduced ejection fraction is loop diuretics and treatment for other conditions the person may have. These manage symptoms but do not reduce hospitalisations for heart failure.

Clinical trial evidence shows that empagliflozin plus standard care reduces the combined risk of dying from cardiovascular causes or likelihood of first hospitalisation for heart failure compared with placebo plus standard care. It is not clear whether empagliflozin plus standard care reduces the likelihood of dying from either any cause or from cardiovascular causes.

There are uncertainties in the economic modelling because of the approach used to model how long people live. It is also uncertain whether the outcomes predicted by the model align with the clinical trial outcomes. Because of this, the cost-effectiveness estimates are uncertain and above what NICE considers a cost-effective use of NHS resources. So, empagliflozin is not recommended.

2 Information about empagliflozin

Marketing authorisation indication

2.1 Empagliflozin (Jardiance, Boehringer Ingelheim) is indicated in adults for 'the treatment of symptomatic chronic heart failure'.

2.2 Empagliflozin is recommended for treating chronic heart failure with reduced ejection fraction in adults (NICE technology appraisal guidance 773).

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for empagliflozin.

Price

2.3 The list price of 10 mg empagliflozin is £36.59 per 28-tablet pack (excluding VAT; BNF online accessed January 2023). The annual treatment cost is £477.30.

3 Committee discussion

The evaluation committee considered evidence submitted by Boehringer Ingelheim, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of condition

3.1 Heart failure is a chronic condition that occurs when the heart is unable to pump enough blood to meet the body's needs. Left ventricular ejection fraction, the amount of blood pumped by the left ventricle during each heartbeat, is one measure used to classify the different types of chronic heart failure, with:

- 40% or less defined as heart failure with reduced ejection fraction

- 41% to 49% defined as heart failure with mildly reduced ejection fraction
- 50% or more defined as heart failure with preserved ejection fraction.

The clinical experts noted that chronic heart failure with reduced ejection fraction and chronic heart failure with preserved or mildly reduced ejection fraction should not necessarily be considered as 2 separate diseases, and that they exist on a continuum. Empagliflozin already has a marketing authorisation for use in people with chronic heart failure with reduced ejection fraction and is recommended by NICE for this population (see NICE's technology appraisal guidance on empagliflozin for heart failure with reduced ejection fraction [TA773]). The committee noted that the population in the NICE scope for this appraisal is 'adults with symptomatic chronic heart failure with a left ventricular ejection fraction of 40% or more'. There is also a group of people with chronic heart failure whose left ventricular ejection fraction was initially below 40% but then improved to above 40%, which is described as heart failure with improved ejection fraction. This evaluation is relevant to people with chronic heart failure with preserved or mildly reduced ejection fraction (left ventricular ejection fraction of more than 40%).

Impact on quality of life

3.2 Symptoms of heart failure with preserved or mildly reduced ejection fraction include difficulty breathing, tiredness and ankle swelling. While treatments are available for heart failure with reduced ejection fraction (see NICE's technology appraisal guidance on dapagliflozin for chronic heart failure with reduced ejection fraction [TA679] and TA773), there are no disease-modifying treatments available for preserved or mildly reduced ejection fraction. The patient experts described how the symptoms, disease severity and impact on daily life of heart failure with preserved or mildly reduced ejection fraction are similar to those experienced by people with reduced ejection fraction. In addition, the lack of hope because of the lack of research and available treatments impacts the quality of life and

mental health of people with heart failure with preserved or mildly reduced ejection fraction. The patient experts explained that because there are no disease-modifying treatments, there is a lack of familiarity with this group in clinical practice, and so they tend to be offered less clinical support. The clinical experts also noted that hospitalisations for heart failure with preserved or mildly reduced ejection fraction place a substantial burden on the NHS. So, a treatment that could reduce the number and duration of hospital stays would be beneficial. The committee concluded that there is an unmet need for people with heart failure with preserved or mildly reduced ejection fraction and a new treatment option for this group would be welcome.

Clinical management

Treatment options

3.3 NICE's guideline on chronic heart failure in adults: diagnosis and management recommends low- to medium-dose loop diuretics (such as furosemide and bumetanide) for people with heart failure with preserved ejection fraction. Specialist treatment advice is recommended for people whose heart failure does not respond to treatment. Symptomatic treatments for comorbidities are also offered to people with heart failure with preserved ejection fraction, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta blockers or mineralocorticoid receptor antagonists (MRAs).

Comparators

3.4 Empagliflozin is expected to be used with current standard care for people with heart failure with preserved or mildly reduced ejection fraction. The final scope for this evaluation listed the comparators as established clinical management without empagliflozin, including but not limited to loop diuretics and symptomatic treatments for comorbidities. The company defined standard care in their model as loop diuretics (furosemide and bumetanide), sacubitril valsartan, ACE inhibitors, ARBs

and MRAs. The EAG noted that sacubitril valsartan does not have a marketing authorisation for heart failure with preserved or mildly reduced ejection fraction in Great Britain and the EAG's clinical experts stated that it would not be used in UK clinical practice. So, the EAG considered that it was not appropriate to include it within the company's basket of standard care treatments. During the clarification stage, a company scenario analysis removed sacubitril valsartan from the standard care treatments and the impact on the cost-effectiveness results was negligible. The committee agreed that the appropriate comparator in this appraisal was standard care, and it was appropriate to model standard care as a basket of treatments.

Clinical effectiveness

Data sources and generalisability

3.5 The company submitted clinical evidence from an international, randomised, double-blind, phase 3 clinical trial (EMPEROR-Preserved). This compared empagliflozin plus standard care and placebo plus standard care in adults (aged 18 years or older) with heart failure with preserved or mildly reduced ejection fraction. The study was done in 23 countries, including 25 people who were randomised and treated in the UK. The study completed in April 2021, with a median follow-up of 26.2 months. In the trial, the mean age was 72 years, about 45% of people were female and about 49% of people had a history of type 2 diabetes. The clinical experts noted that the trial population was about 10 years younger than they would expect in clinical practice, but overall they considered the trial to be generalisable to NHS clinical practice. They noted that, because there are no disease-modifying treatments available for heart failure with preserved or mildly reduced ejection fraction, the standard care treatment arms would be similar across the countries included in the trial. The committee concluded that the results from EMPEROR-Preserved were broadly generalisable to NHS clinical practice.

Trial outcomes

3.6 The primary outcome in EMPEROR-Preserved was the composite outcome of time to cardiovascular death or first hospitalisation for heart failure. Compared with placebo plus standard care, empagliflozin plus standard care reduced the time to occurrence of cardiovascular death or first hospitalisation for heart failure (hazard ratio 0.79, 95% confidence interval 0.69 to 0.90). The committee concluded that empagliflozin significantly reduced the combined risk of cardiovascular death or first hospitalisation for heart failure.

Impact of treatment on cardiovascular and all-cause mortality

3.7 In EMPEROR-Preserved, empagliflozin reduced cardiovascular mortality (hazard ratio 0.91, 95% confidence interval 0.76 to 1.09) compared with placebo, but these results were not statistically significant. Empagliflozin also did not have a statistically significant impact on all-cause mortality (hazard ratio 1.00, 95% confidence interval 0.87 to 1.15). For both all-cause and cardiovascular mortality the confidence intervals crossed 1. This means that it is uncertain whether empagliflozin significantly improved all-cause or cardiovascular mortality compared with placebo. The clinical experts also considered that it was plausible that empagliflozin could reduce cardiovascular mortality, for example, by reducing hospitalisation for heart failure, which is associated with a substantial quality of life burden (see section 3.16) and risk of infection. One clinical expert proposed that reducing hospitalisations may be associated with a reduction in the overall decline in heart function and quality of life that people with chronic heart failure typically experience over time. The clinical experts also noted that the trial population was younger than would be expected in clinical practice (see section 3.5), and that it is possible that an impact on cardiovascular mortality may be seen in an older population. The committee acknowledged that it is plausible that empagliflozin may reduce all-cause and cardiovascular mortality. However, the committee concluded that this is uncertain from the

EMPEROR-Preserved data, because the confidence intervals cross 1 for both all-cause or cardiovascular mortality and the results are not statistically significant.

Economic model

Model structure

3.8 The company modelled the cost effectiveness of empagliflozin using a Markov cohort model with health states defined by Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) quartiles. KCCQ-CSS is a disease-specific measure of quality of life, with higher scores reflecting better health outcomes (less frequent and less severe symptoms). Progression of disease was modelled by transition between health states defined by KCCQ-CSS quartiles. The values used to define each quartile are academic in confidence and cannot be reported here. The model also captured hospitalisation for heart failure as a transient event, and death because of cardiovascular and non-cardiovascular causes through the use of parametric survival equations. It applied a monthly cycle length, with a lifetime horizon, and discounted costs and quality-adjusted life-years (QALYs) at a rate of 3.5% per year. The committee questioned the appropriateness of using health states defined by KCCQ-CSS score. The committee noted that older cost-effectiveness models of chronic heart failure had used health states defined by New York Heart Association score. But, the model structure in this evaluation was similar to those used in previous NICE technology appraisals in chronic heart failure which used health states defined by KCCQ score (see TA679 and TA773). The clinical experts explained that the KCCQ is the most used questionnaire for assessing quality of life in people with chronic heart failure in clinical trials. Published data has demonstrated that KCCQ score is closely correlated with likelihood of hospitalisation for heart failure and cardiovascular death. The committee concluded that the model was similar to those used in previous NICE technology appraisals in chronic heart failure. But, it noted that there are

some uncertainties about the validity of the survival modelling approach (see section 3.10).

Health state transition

3.9 In the company's model, disease progression was modelled by transition between health states defined by KCCQ-CSS score. EQ-5D-5L data was collected in EMPEROR-Preserved at baseline, 12 weeks, 32 weeks, 52 weeks, 100 weeks and 148 weeks. This data was mapped to the EQ-5D-3L and used to derive utility values for each KCCQ-CSS quartile. The company estimated transition probabilities between the KCCQ-CSS quartiles from the raw count KCCQ data collected in EMPEROR-Preserved over 3 time periods (baseline to week 12, week 12 to week 32, and week 32 to week 52). Transition probabilities from week 32 to week 52 were used for the rest of the model time horizon. The transition probabilities were different depending on treatment arm, and people having empagliflozin were more likely to remain in the higher KCCQ states. The company used the last observation carried forward (LOCF) method to impute missing values from visits, which assumes that the missing observation is identical to the previous data point. It noted that the mean scores at weeks 12, 32 and 52 and the distribution of KCCQ-CSS score change from baseline were similar between the imputed and non-imputed datasets. The company also stated that this approach was consistent with previous NICE technology appraisals in chronic heart failure and that it considered that data would be missing at random between the 2 arms (so, there is no systematic difference between missing data in the empagliflozin versus placebo arm). The EAG stated there were enough observations from EMPEROR-Preserved without imputation to provide a robust sample size. It also stated that the number of observations was similar across treatment arms, which suggests that the data were well balanced. The EAG also considered that it was unknown if there might be a systematic difference between the treatment arms affecting whether the values are missing, and therefore considered it more reliable to use the raw non-imputed values. The EAG chose to use

raw non-imputed values, rather than imputed values, in their preferred assumptions, and noted that this led to a substantial increase in the cost-effectiveness estimates. The committee considered that it may be appropriate to use the LOCF approach to impute missing values at time points where KCCQ data was not collected, but that using the LOCF approach to impute missing values at scheduled visits may introduce bias. The committee concluded that it preferred to use the observed values from EMPEROR-Preserved to estimate the transition probabilities used in the model.

Modelling of treatment effect on cardiovascular and all-cause mortality

3.10 The company fitted parametric survival curves to all-cause mortality and to cardiovascular-related mortality Kaplan–Meier data from EMPEROR-Preserved, separately. In the company base case, risk equations for all-cause and cardiovascular mortality were adjusted for treatment effect of empagliflozin and for KCCQ-CSS health state, as a time-updated covariate. The risk of non-cardiovascular death was applied as the maximum risk of non-cardiovascular death from EMPEROR-Preserved (that is, the difference between all-cause and cardiovascular deaths) and the risk of non-cardiovascular deaths in the general population (whichever was greater). General population risk was calculated from the Office for National Statistics 2017 to 2020 life tables for the UK. The company assumed no direct treatment effect of empagliflozin on all-cause mortality. The company stated that this was because the outcome was not statistically significant in EMPEROR-Preserved and a treatment effect of empagliflozin on all-cause mortality was deemed to be clinically implausible. The company did this by setting the empagliflozin treatment effect coefficient for all-cause mortality to zero. The company retained a treatment effect coefficient for empagliflozin on cardiovascular mortality because this was deemed to be clinically plausible, even though the outcome was not statistically significant in EMPEROR-Preserved. The EAG noted that including KCCQ-CSS as a predictor of all-cause and cardiovascular survival generates an indirect survival benefit for

empagliflozin. This is because people having empagliflozin are more likely to remain in better KCCQ-CSS states than people having standard care (see section 3.9), and therefore would have reduced risk of all-cause or cardiovascular death. The EAG and the committee noted that it is not methodologically appropriate to remove a coefficient from a risk equation without refitting the equation and adjusting the other coefficients. The company's cost-effectiveness estimates were uncertain because it should have refitted the all-cause death survival risk equation when it removed treatment effect as a coefficient. The EAG did scenario analyses which assessed the impact of including a direct effect (by including an empagliflozin treatment effect coefficient in the survival model) and/or an indirect effect (by including a KCCQ-CSS treatment effect coefficient) of empagliflozin on cardiovascular and all-cause survival. The committee noted that these scenarios were all done without refitting the survival risk equations, and therefore the resulting cost-effectiveness estimates were uncertain. The committee considered that it may be appropriate to include a direct and indirect treatment effect of empagliflozin on cardiovascular and all-cause mortality, but noted that the model should be able to replicate the observed trial data (see section 3.12). The committee concluded that it would have preferred additional scenarios exploring the impact of a direct and/or indirect treatment effect of empagliflozin on cardiovascular and all-cause mortality, which refitted the survival model when parameters were excluded (for example, coefficient for treatment effect and impact of KCCQ state).

Survival extrapolations

3.11 To model cardiovascular and all-cause survival beyond the observed data in EMPEROR-Preserved, the company fitted a joint Weibull model, which assumes proportional hazards. The company stated that for all-cause mortality, the Weibull model was the best-fitting distribution and provided the most clinically plausible long-term survival estimates. The company also used the Weibull model for cardiovascular mortality to ensure alignment between all-cause and cardiovascular mortality. It provided

scenario analyses using alternative parametric models to extrapolate cardiovascular and all-cause mortality. The EAG considered that it was inappropriate to assume proportional hazards, because it is implausible that there would be a constant treatment effect throughout the trial and extrapolated period. It also noted that the long-term overall survival extrapolations are uncertain. The committee noted that using alternative parametric models to extrapolate all-cause and cardiovascular mortality increased the incremental cost-effectiveness ratio (ICER). It noted that there is uncertainty regarding the method used to incorporate treatment effect on survival in the model (see sections 3.10 and 3.12), and so concluded that it cannot select a preferred extrapolation until this uncertainty has been resolved. The committee considered that it would be helpful to see the cost-effectiveness results with different parametric survival extrapolations, after scenarios assessing the impact of direct and indirect treatment effects on all-cause and cardiovascular survival have been done (see section 3.10).

Ability of the model to replicate observed all-cause and cardiovascular survival outcomes

3.12 The committee noted that including a time-updated model covariate and a treatment effect coefficient (see section 3.10) is not a standard modelling approach and could affect model validity. While this approach was used in previous NICE appraisals of sodium-glucose-co-transporter 2 (SGLT2) inhibitors (see TA679 and TA773), it is not commonly used in other disease areas. The committee noted that a patient-level multi-state simulation model may have been more appropriate, because it generates a patient history and considers competing risks. The company said it considered a patient-level multi-state simulation model, but noted that in the NICE technology appraisal guidance on sacubitril valsartan for treating symptomatic chronic failure with reduced ejection fraction the committee preferred a Markov model. The committee noted that survival extrapolations of all-cause and cardiovascular mortality had been provided, but that these were the outputs of the regression analysis,

rather than the economic model survival outcomes (including the indirect impact of changes in KCCQ-CSS state over time). At the clarification stage of the evaluation, the company provided a table comparing the total number of cardiovascular deaths observed in EMPEROR-Preserved at 26 weeks, 26 months and 3 years with the total number of cardiovascular deaths predicted by the cost-effectiveness model at each time point. The company noted that there were some differences in the number of cardiovascular deaths observed in EMPEROR-Preserved and predicted in the model, but considered that the differences in cardiovascular deaths between the empagliflozin and placebo arms were similar in the observed and predicted data. It suggested that this meant that the incremental results of the model were likely to still be valid. The committee was concerned that the model predictions did not align with the observed data from EMPEROR-Preserved. The committee noted that a model that does not replicate the observed trial data to an appropriate level of accuracy would lead to considerable uncertainty around the plausibility of the model results. The committee concluded that a comparison of the overall survival and cardiovascular survival predictions from the economic model (which includes the impact of the changes in KCCQ-CSS state over time) and the observed data from EMPEROR-Preserved is needed to determine whether the modelling approach was reasonable.

Modelling of treatment effect on hospitalisation for heart failure

3.13 The company used count data from EMPEROR-Preserved to model the number of hospitalisations for heart failure in the model. The monthly rate of hospitalisations for heart failure was estimated using a Poisson model with time-varying KCCQ-CSS states and treatment received as predictors. In the company base case, the rates of hospitalisation for heart failure were modelled to be constant in each treatment arm, respectively. The company's approach did not differentiate between initial and subsequent hospitalisations. The EAG considered that it would be more robust to use Kaplan–Meier data to estimate hospitalisation for heart failure. This would have allowed extrapolation of hospitalisation for heart failure events over

the model time horizon, meaning the company would not need to assume a constant rate of hospitalisations for heart failure. The EAG also noted that EMPEROR-Preserved showed that empagliflozin had a larger impact on preventing first heart failure events than on second events. The EAG considered that it is likely that empagliflozin does not have a benefit in preventing subsequent hospitalisations. So, by considering all events in the trial as first events, the model overestimates the benefit of empagliflozin. The EAG noted that the absolute number of hospitalisations for heart failure in the model is considerably overestimated compared with the number of hospitalisations observed in EMPEROR-Preserved over the same time period. Also, the overestimation increases as time progresses in the model and the model increasingly overestimates the benefit associated with empagliflozin. So, the EAG is uncertain whether hospitalisations for heart failure are accurately estimated over the model time horizon. The EAG was also uncertain about the company's process and rationale for selecting the final variables included in the risk equations for hospitalisation for heart failure. The committee considered that it was unlikely that the risk of hospitalisation for heart failure would be constant over time. It was concerned that the model did not align with the trial data (see section 3.12) and so lacked confidence in the resulting cost-effectiveness estimates. The committee concluded that a comparison of the hospitalisation for heart failure predictions from the economic model (including the impact of changes in KCCQ-CSS state over time) and the observed data from EMPEROR-Preserved is needed to determine whether the modelling approach was appropriate.

Long-term treatment effect

3.14 The company estimated transition probabilities between KCCQ-CSS quartiles from trial data for 3 time periods (see section 3.9). On discontinuation of empagliflozin, transition probabilities for standard care were used from then onwards. The company and clinical experts stated that they would not expect a sustained treatment effect of empagliflozin after discontinuation. The EAG noted that the model structure results in a

sustained treatment effect over time. This is because there is a low probability of moving health states from month 9 onwards, and at month 8 a higher percentage of people having empagliflozin were in the higher KCCQ-CSS states. People in higher KCCQ-CSS states have better modelled quality of life. They also have reduced risk of hospitalisation and mortality, because the risk of these is dependent on KCCQ state (see sections 3.10 and 3.13). The company did scenario analyses to explore the uncertainty regarding a potential sustained treatment effect of empagliflozin. This included a scenario in which the transition probabilities between KCCQ-CSS quartiles for the empagliflozin arm were set to transition probabilities for the standard care arm after 8 months. This scenario significantly increased the cost-effectiveness estimates. The EAG noted that this scenario was likely to be overly pessimistic. The committee concluded that the model structure may contribute to a sustained treatment effect for empagliflozin, which may bias the cost-effectiveness results in favour of empagliflozin.

Utility values

Source of utility values and use in the model

3.15 EQ-5D-5L data collected in EMPEROR-Preserved was mapped to EQ-5D-3L and used to derive utility values for each KCCQ-CSS quartile (see section 3.9), using a mixed-effect linear regression analysis. The company used a multiplicative approach for deriving utility estimates, as recommended in in NICE's Decision Support Unit technical support document 12. The utility estimated in the mixed-effects model for quartile 4 (the least severe quartile) was higher than the utility seen in the UK general population reported by Sullivan et al. (2011) for the age group of 70 years to 79 years. So, the company used the utility reported in Sullivan et al. (0.7230) for quartile 4 and adjusted the utility values for quartiles 1 to 3 based on the relative difference between the estimated utility for quartile 4 and the value reported in Sullivan et al. At the clarification stage of the evaluation, the EAG requested that the company

included age-related utility decrements, using the algorithm published by Ara and Brazier (2010), which led to a small increase in the cost-effectiveness estimates. The EAG preferred the use of age-related utility decrements in its base case. The committee concluded that the EAG's approach of using age-adjusted utilities is more appropriate.

Duration of impact of heart failure events on quality of life

3.16 The company used a disutility period of 1 year for heart failure events in its base case; that is, being hospitalised for heart failure would reduce a person's quality of life for 1 year after the event. The company noted that this aligned with the assumption accepted by the committee in TA679. The EAG noted that the disutility applied for each hospitalisation for heart failure was higher than in TA773. The EAG noted that the mean length of stay in hospital in EMPEROR-Preserved was 11 days. The EAG's clinical experts suggested being hospitalised for 1 day would impact quality of life for 1 week, with a maximum duration of impact on quality of life of 6 months after discharge. So, the EAG base case ranged between scenarios with disutility periods of 11 weeks and of 6 months. The company stated that the data from EMPEROR-Preserved and other trials showed that hospitalisation for heart failure impacts quality of life for 1 year. The clinical experts stated that a hospitalisation for heart failure has a substantial impact on quality life and that for older people a hospital stay can impact on frailty, mobility and risk of falls. They considered that a disutility period of 11 weeks was an underestimate and that heart failure impacted quality of life for around 6 months. The committee concluded that it was reasonable to assume that a hospitalisation for heart failure impacted quality of life for 6 months.

Costs

Resource use estimate for hospitalisation for heart failure events

3.17 The company estimated the acute costs of hospitalisation for heart failure based on NHS reference costs from 2019/2020 (inflated to 2021 values)

for non-elective long inpatient stay. These were calculated as the weighted average of reference costs for healthcare resource group (HRG) codes (EB03A to EB03E) and the number of finished consultant episodes. The mean duration of a hospitalisation for heart failure in EMPEROR-Preserved was 11 days (median: 8 days; quartile 3: 13 days). The EAG noted that the company had included more severe cost codes in their weighted average, for example, EB03A is associated with a 53-day hospital stay. The EAG preferred the scenario using the HRG code EB03E only, which is associated with a 13-day hospital stay, and used this in their base-case cost-effectiveness estimates. This led to a small increase in the ICER. The committee acknowledged the clinical experts' opinion that the length of hospital stay can vary. The committee concluded that it was more appropriate to use the less severe EB03E code, rather than the weighted average including more severe codes.

Cost of cardiovascular deaths

3.18 The company estimated the cost of cardiovascular death based on a regression analysis presented in Alva et al. (2014) which estimated the added inpatient costs for type 2 diabetes complications from a UK cohort. The regression analysis reported coefficients, including age and sex, for the impact of cardiovascular death on inpatient hospitalisation costs. The company used age and sex data from EMPEROR-Preserved to calculate an average cost of £4,295 per cardiovascular death. This approach aligned with TA773. The EAG noted that the cost estimates in Alva et al. related to the additional costs of type 2 diabetes complications for hospitalisations. It preferred the scenario using the absolute cost of cardiovascular events reported in Alva et al., rather than using the estimates from the regression analysis, because the model is not considering these events as type 2 diabetes complications. This decreased the cost of cardiovascular death to £3,809. The EAG also noted that a substantial number of deaths in EMPEROR-Preserved were sudden cardiac deaths. It preferred the company's scenario which took a conservative approach of assuming that the cost of sudden cardiac death

was £0. This reduced the total cost of cardiovascular deaths to £1,452. The committee concluded that it preferred the more conservative approach of using absolute values from Alva et al. and assuming that the cost of sudden cardiac death was £0.

Estimation of annual GP visits

3.19 The company's model assumed that people with heart failure with preserved or mildly reduced ejection fraction would have a total of approximately 12 GP visits or contacts per year. The committee noted that GPs may not frequently see people with heart failure with preserved or mildly reduced ejection fraction because there are no disease-modifying treatments available for this population (see section 3.3). It noted that other healthcare professionals, such as specialist pharmacists and nurses, may also be involved in the care pathway. The committee concluded that 6 primary care visits per year was a reasonable estimate.

Adverse events

Modelling of adverse events

3.20 In the company's model the risk of experiencing adverse events was informed by the most common adverse events of special interest in EMPEROR-Preserved. This assumed a constant hazard and different rates for each treatment arm. The EAG had no comments on this approach. The committee concluded that the company's approach of modelling adverse events was appropriate.

Severity

3.21 NICE's health technology evaluations manual notes that when considering overall benefits, the committee can consider decision-making modifiers. The severity modifier allows the committee to give more weight to health benefits in the most severe conditions. The company did not consider it appropriate to apply a severity modifier for heart failure with preserved or

mildly reduced ejection fraction. The committee agreed that it was not appropriate to include a severity modifier for this population.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.22 The company's base-case deterministic ICER was £14,429 per QALY gained. The EAG applied the following assumptions in its base case:

- observed data for KCCQ-CSS transition probabilities, without imputation (see section 3.9)
- age-related decrements from Ara and Brazier 2010 (see section 3.15)
- HRG code cost (EB03E) associated with less severe hospitalisation for heart failure (13-day hospital stay; see section 3.17)
- unit cost for cardiovascular death of £1,452, including cost of sudden cardiovascular death as £0 (see section 3.18).

In addition, the EAG was uncertain whether it was appropriate to assume a treatment effect of empagliflozin on cardiovascular and all-cause deaths (see section 3.10). It was also uncertain whether the disutility period after a hospitalisation for heart failure would last for 11 weeks or 6 months (see section 3.16). So, the EAG provided a range of base-case deterministic ICERs. The EAG's cost-effectiveness estimates are considered to be commercial in confidence by the company and cannot be reported here. The committee noted that all of the EAG's base case ICERs were above £30,000 per QALY, and some were substantially above this. The EAG also did scenario analyses which assessed the impact of including a direct effect and/or an indirect effect of empagliflozin on cardiovascular and all-cause deaths. The committee noted that these scenarios were all done without refitting the survival risk equations, and therefore the resulting cost-effectiveness estimates were uncertain (see section 3.10). Also, the committee recalled that there were significant uncertainties in the company's approach to modelling the treatment effect on cardiovascular and all-cause deaths (see section 3.12).

Committee preferred assumptions

3.23 The committee's preferred assumptions were to use:

- observed data for KCCQ-CSS transition probabilities, without imputation (see section 3.9)
- age-related decrements from Ara and Brazier 2010 (see section 3.15)
- hospitalisation for heart failure disutility applied for 6 months (see section 3.16)
- HRG code cost (EB03E) associated with less severe hospitalisation for heart failure (13-day hospital stay; see section 3.17)
- unit cost for cardiovascular death of £1,452, including cost of sudden cardiovascular death as £0 (see section 3.18)
- 6 annual GP visits (see section 3.19).

The committee considered that it was uncertain whether it was appropriate to assume a treatment effect of empagliflozin on cardiovascular and all-cause deaths (see section 3.10). To resolve some of the uncertainties related to the modelling of survival, the committee would have preferred to see:

- Evidence that the model can reproduce the outcomes observed in EMPEROR-Preserved. For example, a comparison of observed outcomes in the trial (such as cardiovascular and all-cause mortality, and hospitalisations caused by heart failure) versus model outcomes. This would need to be survival data specifically produced within the model (as opposed to the regression analysis), and include the impact of changing KCCQ-CSS health states on survival.
- Scenarios exploring the exclusion of a direct and/or indirect treatment benefit for empagliflozin on cardiovascular and all-cause deaths, with refitting of the survival model whenever parameters are excluded (for example, coefficient for treatment effect).

Committee cost-effectiveness estimates

3.24 The committee noted that with its preferred assumptions to modelling survival (see section 3.23), the cost-effectiveness estimates were above £20,000 per QALY gained. The lower bound of the threshold (£20,000 to £30,000 per QALY gained) was preferred by the committee given the large impact of the uncertainties relating to survival estimates on the ICER.

Other factors

Equality issues

3.25 The committee noted that previous NICE technology appraisals in chronic heart failure had identified that people from Black or South Asian family backgrounds may have a higher risk of developing heart failure. In addition, a meta-analysis of data from people with chronic heart failure with reduced ejection fraction (Zannad et al. [2020]) suggested that SGLT2 inhibitors were more effective in people from Black or Asian family backgrounds. The committee noted that there is not strong evidence from EMPEROR-Preserved to suggest that empagliflozin was more effective at treating chronic heart failure with preserved or mildly reduced ejection fraction in people from Black or Asian family backgrounds. But, it noted that clinical trials were not usually powered to detect differences by family background. The committee concluded that there was insufficient evidence to determine whether empagliflozin was more or less effective in people from Black or Asian family backgrounds. The committee noted that its recommendation applied to all people, regardless of family background. The committee concluded that differences in prevalence or incidence of a disease cannot be addressed in a technology appraisal.

Prescribing setting

3.26 NICE's guideline on chronic heart failure in adults: diagnosis and management recommends that a specialist heart failure multidisciplinary team should work in collaboration with the primary care team to start new medicines that need specialist supervision. Empagliflozin is currently

prescribed for heart failure with reduced ejection fraction in primary care, according to the advice of a heart failure specialist. The company noted that socioeconomic deprivation is a strong risk factor for developing heart failure and experiencing adverse heart failure outcomes. The company suggested that inequality in access to specialist care across the UK may contribute to these health inequalities. So, broad prescribing of empagliflozin in primary and secondary care may reduce health inequalities. Also, the requirement for advice from a heart failure specialist may delay access to treatment and contribute to resource constraints. The patient experts explained that many GPs are not familiar with heart failure with preserved or mildly reduced ejection fraction, because there are currently no disease-modifying treatments available for this population. The committee noted that GPs are experienced in prescribing empagliflozin for chronic heart failure with reduced ejection fraction and for type 2 diabetes. The committee also noted that clinicians have experience in treating chronic heart failure with reduced ejection fraction and type 2 diabetes across primary and secondary care. The committee discussed the capacity challenges facing GPs around the diagnosis of heart failure with preserved or mildly reduced ejection fraction. It noted that NICE's guideline on chronic heart failure in adults: diagnosis and management recommends the measurement of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in people with suspected heart failure, followed by specialist assessment and transthoracic echocardiography. The committee concluded that if empagliflozin was recommended, it would be started on the advice of a heart failure specialist who can determine the most appropriate treatment.

Conclusion

Recommendation

3.27 The committee concluded that when its preferred assumptions are incorporated, the cost-effectiveness estimates for empagliflozin are higher than what NICE considers a cost-effective use of NHS resources.

Therefore, the committee did not recommend empagliflozin for the treatment of chronic heart failure with preserved or mildly reduced ejection fraction in the NHS.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

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

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

Chair

Stephen O'Brien

Chair, technology appraisal committee C

NICE project team

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

Raphael Egbu and Lizzie Walker

Technical leads

Christian Griffiths

Technical adviser

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Project manager

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