NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Dapagliflozin 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 dapagliflozin 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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using dapagliflozin in the NHS in England.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 Dapagliflozin 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 dapagliflozin 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 dapagliflozin 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 dapagliflozin 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 are likely to be above what NICE considers a cost-effective use of NHS resources. So, dapagliflozin is not recommended.

2 Information about dapagliflozin

Marketing authorisation indication

2.1 Dapagliflozin (Forxiga, AstraZeneca) is indicated in adults for 'the treatment of symptomatic chronic heart failure'.

2.2 Dapagliflozin is recommended for treating chronic heart failure with reduced ejection fraction in adults (NICE technology appraisal guidance 679).

Dosage in the marketing authorisation

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

Price

2.3 The list price of 10 mg dapagliflozin 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 AstraZeneca, 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. Dapagliflozin 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 dapagliflozin for heart failure with reduced ejection fraction [TA679]). 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 is initially below 40% but then improves to above 40%; these were included as a subgroup in the DELIVER clinical trial (see section 3.5). 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 TA679 and NICE's technology appraisal guidance on empagliflozin for heart failure with reduced ejection fraction [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 inhibitors, angiotensin II receptor blockers, beta blockers or mineralocorticoid receptor antagonists.

Comparators

3.4 Dapagliflozin is expected to be used with 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 dapagliflozin, 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). The EAG noted that the company did not include

symptomatic treatments for comorbidities in its economic modelling. But, it considered that this was unlikely to impact the cost-effectiveness estimates and stated that the company's choice of comparators was appropriate. The committee agreed that the appropriate comparator in this appraisal was standard care, and it was appropriate to model standard care as loop diuretics.

Clinical effectiveness

Data sources and generalisability

3.5 The company submitted clinical evidence from a randomised, double-blind, phase 3 clinical trial (DELIVER). This compared dapagliflozin plus standard care and placebo plus standard care in adults (40 years and over) with heart failure with preserved or mildly reduced ejection fraction. The study was done in 20 countries from Europe, Asia and North America but did not include UK patients. The study completed in March 2022. In the trial, the mean age was 72 years, about 44% of people were female and about 45% of people had a history of type 2 diabetes. About one-fifth of people in the trial had been previously diagnosed with heart failure with reduced ejection fraction (left ventricular ejection fraction of 40% or less) which had improved (left ventricular ejection fraction over 40%). Participants in DELIVER had not had a sodium-glucose-co-transporter 2 (SGLT2) inhibitor, such as dapagliflozin, for at least 4 weeks before randomisation. 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. The committee questioned whether DELIVER would be generalisable to UK practice because it did not include any UK participants. The clinical experts noted that the North American population in DELIVER is likely generalisable to UK 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 DELIVER were broadly generalisable to NHS clinical practice.

Trial outcomes

3.6 The primary outcome in DELIVER was the composite outcome of time to cardiovascular death or first heart failure event (hospitalisation caused by heart failure or urgent heart failure visit). Compared with placebo plus standard care, dapagliflozin plus standard care reduced the time to cardiovascular death or first heart failure event (hazard ratio 0.82, 95% confidence interval 0.73 to 0.92). The committee concluded that dapagliflozin significantly reduced the combined risk of cardiovascular death or first heart failure event.

Impact of treatment on cardiovascular and all-cause mortality

3.7 In DELIVER, dapagliflozin reduced all-cause mortality (hazard ratio 0.94, 95% confidence interval 0.83 to 1.07) and cardiovascular mortality (hazard ratio 0.88, 95% confidence interval 0.74 to 1.05) compared with placebo, but these results were not statistically significant. For both all-cause and cardiovascular mortality the confidence intervals crossed 1. This means that it is uncertain whether dapagliflozin significantly improved all-cause or cardiovascular mortality compared with placebo. The clinical experts noted that the clinical trial was not powered to assess the impact of dapagliflozin on all-cause or cardiovascular mortality. They highlighted a pre-specified analysis which pooled results from DELIVER with trial results from people with reduced ejection fraction (DAPA-HF). This pooled analysis showed that dapagliflozin significantly reduced cardiovascular mortality compared with placebo (hazard ratio 0.86, 95% confidence interval 0.76 to 0.96; Jhund et al. [2022]). In this pooled analysis there was no evidence that the effect of dapagliflozin differed by level of ejection fraction. The committee noted that evidence from the pooled analysis was not incorporated into the economic model. The clinical experts considered that it was plausible that dapagliflozin could reduce cardiovascular mortality by reducing hospitalisation for heart failure, which is associated

with a substantial quality of life burden (see section 3.2) 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 dapagliflozin may reduce all-cause and cardiovascular mortality. However, the committee concluded that this is uncertain from the DELIVER data, because the confidence intervals cross 1 for both all-cause or cardiovascular mortality and the results are not statistically significant.

Trial outcomes in people with heart failure with improved ejection fraction

3.8 DELIVER included a subgroup of people whose left ventricular ejection fraction was initially below 40% but had improved to above 40% (heart failure with improved ejection fraction; see section 3.5). To further understand the impact of dapagliflozin on cardiovascular and all-cause deaths, the EAG requested subgroup analyses for people with heart failure with improved ejection fraction and people who had consistent left ventricular ejection fraction of 40% or more. It noted that the treatment effect of dapagliflozin on survival was different in the 2 groups. The magnitude of difference is deemed academic in confidence by the company and cannot be reported here. The EAG considered whether any benefits in survival could be driven by the impact in the heart failure with improved ejection fraction group. Clinical expert opinion sought by the EAG suggested that in clinical practice, people with heart failure with reduced ejection fraction would be eligible for SGLT2 inhibitors (including dapagliflozin) and would be unlikely to stop treatment when their left ventricular ejection fraction increased to above 40% (heart failure with improved ejection fraction). The company highlighted that DELIVER only

included people who had not had an SGLT2 inhibitor within 4 weeks before randomisation. It also noted that DELIVER included people with heart failure with improved ejection fraction to understand the treatment effect of dapagliflozin on this subgroup because there were no previous studies for this subgroup. The committee acknowledged the company's and EAG's perspectives and concluded that it would take both into account in its decision making.

Economic model

Model structure

3.9 The company modelled the cost effectiveness of dapagliflozin using a Markov cohort model with health states defined by Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ-TSS) quartiles. KCCQ-TSS 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 KCCQ quartiles (KCCQ-TSS scores of 0 to below 55, quartile 1; 55 to below 73, quartile 2; 73 to below 88, quartile 3; 88 to 100, quartile 4). 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 used a monthly cycle length, with a lifetime horizon (to 101 years), 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-TSS 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 that 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 3.13).

Health state transition

3.10 In the company's model, disease progression was modelled by transition between health states defined by KCCQ-TSS score. EQ-5D-5L data was collected in DELIVER at baseline, 8 months and at the final visit. This data was mapped to the EQ-5D-3L and used to derive utility values for each KCCQ-TSS quartile. The company estimated transition probabilities between the KCCS-TSS quartiles from the raw count KCCQ data collected in DELIVER over 2 time periods (baseline to month 4 and month 5 onwards). Transition probabilities from month 5 onwards were used for the rest of the model time horizon. The transition probabilities were different depending on treatment arm, and people having dapagliflozin were more likely to remain in the higher KCCQ states. The company used monthly transition count data from DELIVER to obtain transition probabilities between health states. For months that KCCQ data was unavailable, the company used a last observation carried forward (LOCF) approach. That is, people remained in the same KCCQ quartile until further data showing they had moved to a different health state became available. At the clarification stage, the company noted that LOCF was not used for people whose data were missing at the scheduled assessment, and the data were not imputed in that situation. It noted that the same modelling approach was applied in TA679. The EAG considered that the use of LOCF is reasonable if it is not used after people in the trial have missed one of the scheduled KCCQ-TSS measurements, because this could lead to bias. The committee concluded that the company's imputation method was appropriate.

Modelling of treatment effect on cardiovascular and all-cause mortality

3.11 The company fitted parametric survival curves to all-cause mortality and to cardiovascular-related mortality Kaplan–Meier data from DELIVER, separately. In the company base case, risk equations for all-cause and cardiovascular mortality were adjusted for treatment effect of dapagliflozin, KCCQ-TSS health state (time-updated covariate), age, sex, body mass index, race, left ventricular ejection fraction, N-terminal pro-B-type natriuretic peptide (NT-proBNP), systolic blood pressure, type 2 diabetes, atrial fibrillation, history of hospitalisation for heart failure and heart failure duration. The risk of non-cardiovascular death was applied as the maximum risk of non-cardiovascular death from DELIVER (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 by adjusting data in the Office for National Statistics 2017 to 2019 life tables for England and Wales with cardiovascular mortality risk data reported by the World Health Organization. The EAG noted that including KCCQ-TSS as a predictor of all-cause and cardiovascular mortality generates an indirect survival benefit for dapagliflozin. This is because people having dapagliflozin are more likely to remain in better KCCQ-TSS states than people having standard care (see section 3.15), and therefore would have reduced risk of all-cause or cardiovascular death. Because it is uncertain whether dapagliflozin reduced cardiovascular or all-cause mortality in DELIVER (see section 3.7), the EAG requested that the company do a scenario analysis in which the treatment effect of dapagliflozin on cardiovascular and all-cause deaths is excluded from the survival estimates. The company considered the additional scenario requested by the EAG inappropriate, noting that the use of cardiovascular and all-cause mortality data from DELIVER is the most robust method for estimating survival. It also expressed that any additional uncertainty related to dapagliflozin treatment effect on survival would already be captured in the probabilistic sensitivity analysis. The EAG excluded the direct treatment effect of

dapagliflozin on cardiovascular and all-cause deaths in its base-case assumptions, which had a large impact on the cost-effectiveness estimates. The EAG also did scenario analyses in which it assessed the impact of including a direct effect (by including a dapagliflozin treatment effect coefficient in the survival model) and/or an indirect effect (by including a KCCQ-TSS treatment effect coefficient) of dapagliflozin on cardiovascular and all-cause survival. The EAG did this by setting the dapagliflozin treatment effect coefficient and/or the KCCQ coefficient in the model to zero. 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, and therefore the resulting cost-effectiveness estimates were uncertain. The committee considered that it may be appropriate to include a direct and/or indirect treatment effect of dapagliflozin on cardiovascular and all-cause mortality, but noted that the model should be able to replicate the observed trial data (see section 3.13). The committee concluded that it would have preferred additional scenarios exploring the impact of a direct and/or indirect treatment effect of dapagliflozin 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

3.12 To model cardiovascular and all-cause survival beyond the observed data in DELIVER, the company used a piecewise modelling approach with an inflection point at 1 year. The company considered DELIVER survival data too complex for a single fully parametric model to be applied and noted that there was a clear separation of the dapagliflozin and placebo curves, beginning at 1 year. Taking into account visual and statistical fit, the company selected the adjusted Weibull model for both cardiovascular and all-cause survival extrapolation for its base case. The company provided scenario analyses using alternative parametric models to extrapolate cardiovascular and all-cause mortality. The EAG raised concerns about

the choice of survival curves, noting that the adjusted Gompertz model was the only clinically plausible model for fitting cardiovascular survival data, and that the other models produced optimistic results (that is, underestimated cardiovascular mortality). The EAG considered the adjusted Weibull and Gompertz to both be clinically plausible for estimating all-cause survival. The company attempted to externally validate its survival extrapolation by comparing it to 2 published studies which reported 5- and 10-year survival in people with heart failure (Jones et al. [2019]) and Shahim et al. [2021], respectively). For the analyses, it reweighted the baseline characteristics for people having placebo treatment in DELIVER and compared all-cause mortality in this group to the published data. The EAG noted that the validation with Shahim et al. (2021) produced inconsistent results because the Gompertz model fitted best at year 5 while the Weibull fitted best at year 10. It also highlighted that neither of the published studies reported data beyond 10 years. The EAG explored a scenario using the Gompertz model for cardiovascular and all-cause mortality, which increased the incremental cost-effectiveness ratio (ICER). In addition, the EAG considered that the company did not provide a clinically plausible rationale for the inflection point and noted that the piecewise approach may have contributed to the poor model fit. It would have preferred the use of a single fully fitted parametric model for extrapolating survival. The committee noted that using the Gompertz model to extrapolate both all-cause and cardiovascular mortality increased the ICER, but it considered that the Gompertz model was likely overly pessimistic. It noted that there is uncertainty regarding the method used to incorporate treatment effect on survival in the model (see section 3.11) 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/or indirect treatment effect

on all-cause and cardiovascular survival have been done (see section 3.11).

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

3.13 The committee noted that including a time-updated model covariate and a treatment effect coefficient (see section 3.11) is not a standard modelling approach and could affect model validity. While this approach was used in previous NICE appraisals of 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. It 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-TSS state over time). The committee also noted that a model that does not replicate the 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 changes in KCCQ-TSS state over time) and the observed data from DELIVER, is needed to determine whether the modelling approach was reasonable.

Modelling of treatment effect on heart failure events

3.14 The company modelled hospitalisation for heart failure and urgent hospitalisation for heart failure by applying generalised estimating equations to DELIVER data. It derived two sets of equations, one fully adjusted for patient characteristics and treatment effect (referred to as adjusted) and another which was only adjusted for treatment effect (referred to as unadjusted). The adjusted model was used in the company's base case. The company's approach assumed a constant risk

of hospitalisation for heart failure and did not differentiate between initial and subsequent hospitalisations. The EAG noted that DELIVER data did not convincingly support a benefit of dapagliflozin in reducing urgent hospitalisation for heart failure. So, the EAG excluded a dapagliflozin treatment effect on urgent hospitalisation for heart failure in its base case. The committee concluded that a comparison of the hospitalisation for heart failure predictions from the economic model (including the impact of changes in KCCQ-TSS state over time) and the observed data from DELIVER is needed to determine whether the modelling approach was appropriate.

Long-term treatment effect

3.15 The company estimated transition probabilities between KCCQ-TSS quartiles from trial data for 2 time periods. On discontinuation of dapagliflozin, 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 dapagliflozin 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 5 onwards, and at month 4 a higher percentage of people having dapagliflozin were in the higher KCCQ-TSS states. The committee concluded that the model structure may contribute to a sustained treatment effect for dapagliflozin, which may bias the cost-effectiveness results in favour of dapagliflozin.

Utility values

Source of utility values and use in the model

3.16 EQ-5D-5L collected in DELIVER was mapped to EQ-5D-3L and used to derive utility values for each KCCQ-TSS quartile (see section 3.10). The EAG questioned the company's method for deriving utility estimates, noting that an additive approach was used rather than the preferred multiplicative approach outlined in NICE's Decision Support Unit technical

support document 12. It noted that the mean utility applied for quartile 4 (the least severe quartile) in the company's economic model was higher than the general population utility of the same age. Additionally, the EAG highlighted that the company did not include the impact of age on utility because it considered this to be negligible. The EAG highlighted clinical expert opinion which considered it implausible for people with symptomatic heart failure with preserved or mildly reduced ejection fraction to have a better quality of life than the general population of the same age. So, for its base case, the EAG used the multiplicative approach to derive its utility, adjusting for age impact and setting quartile 4 utility to equal the general population. The committee concluded that the EAG's approach for deriving utility estimates is more appropriate.

Duration of impact of heart failure events on quality of life

3.17 The company used a disutility period of 1 month for heart failure events in its base case; that is, being hospitalised for heart failure would reduce people's quality of life for 1 month. The EAG's clinical experts suggested that the average hospital stay for a heart failure event was about 11 days. It considered that 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 company did scenario analyses assuming a disutility period of 2.75 months (11 weeks) and 6 months, which improved its cost-effectiveness estimates. The EAG base case used a disutility period of 11 weeks. The clinical experts stated that a hospitalisation for heart failure has a substantial impact on quality of 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

Non-elective care costs

3.18 The company estimated the costs of non-elective care, including hospitalisation for heart failure and inpatient care for adverse events, using NHS reference costs from 2020/2021. The EAG noted that the cost of non-elective care was markedly higher in 2020/2021 compared with recent years and considered that COVID-19 may have influenced the cost. So, the EAG asked the company to provide a scenario in which non-elective inpatient care was costed using NHS reference costs from 2019/2020, inflated to 2020/2021, which increased the cost-effectiveness estimates. The EAG preferred the use of the inflated values and applied this in its base case. The committee concluded that both sources of NHS reference costs were plausible, and it was uncertain which NHS reference cost values were most appropriate, given the uncertain impact of the COVID-19 pandemic.

Resource use estimate for hospitalisation for heart failure events

3.19 The company estimated the acute costs of hospitalisation for heart failure based on NHS reference costs from 2020/2021 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). The EAG's clinical experts considered that the average length of hospital stay for heart failure was 11 days. The company did not provide data on the average duration of hospital stay in DELIVER, noting that there were regional differences in the clinical trial which could introduce uncertainty. 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

3.20 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 company used the cost associated with a myocardial infarction, because this was the lowest cost of the available fatal cardiovascular events. This cost was then inflated to the 2020/2021 cost year to give a cost of £1,763 per cardiovascular event. This approach was aligned with that used in TA679. The EAG noted that sudden cardiovascular deaths may be associated with a lower cost per event, but that only a small proportion of people in DELIVER experienced sudden cardiovascular deaths. The committee concluded that the company's approach was appropriate.

Estimation of annual GP visits

3.21 The company's model assumed that people with heart failure with preserved or mildly reduced ejection fraction would have a total of 23.14 GP visits or other contacts per year. The company clarified that the number of GP visits or contacts in the model included other primary care visits, but that it had conservatively costed these all as GP visits. The EAG noted that because of fewer treatments being available for this group (see section 3.3), approximately 6 GP or other primary care visits would be expected per year. It asked the company to explore a scenario with 6 GP visits per year, which improved the cost-effectiveness estimates. 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 GP or other primary care visits per year was a reasonable estimate.

Adverse events

Inclusion of amputation as an adverse event

3.22 The company's base case included adverse events reported in DELIVER which occurred with a frequency of over 1%. Amputation occurred with a frequency of less than 1% in DELIVER but was also included in the model. The company took this approach because amputation is an adverse event of interest because of the historical link between SGLT2 inhibitors and risk of amputation. The company also noted that a recent meta-analysis on SGLT2 inhibitors and the risk of amputation suggests that this link is not statistically significant. The EAG highlighted that clinical expert opinion suggests that dapagliflozin is not expected to be associated with increased risk of amputation. So, it considered any increased risk of amputation to be confounded by the presence of type 2 diabetes mellitus. The EAG requested that the company stratify the amputation events in DELIVER based on type 2 diabetes status, also noting that in UK clinical practice, people with type 2 diabetes are eligible for treatment with dapagliflozin. The EAG noted that the requested analysis did not support the inclusion of amputation in the cost-effectiveness modelling. Given the potential for confounding results, the EAG's preference was to exclude amputation as an adverse event in its base-case assumptions. The committee heard from clinical experts that there is unlikely to be a link between SGLT2 inhibitors and amputation. Patient experts also noted that they were unfamiliar with this risk. The committee considered that dapagliflozin was unlikely to be associated with an increased risk of amputation and concluded that the EAG's approach was reasonable.

Estimation of adverse event probabilities

3.23 The company derived adverse event probabilities based on data from DELIVER trial. The EAG noted that the adverse event probabilities used in the company's model were higher than those seen in TA679 and lacked external validity. While it expected some differences in the adverse event probabilities because people in DELIVER were about 5 years older, and therefore had more comorbidities, the size of difference is higher than expected. The company considered that comparing DELIVER and DAPA-HF (which included people with heart failure with reduced ejection fraction) introduces uncertainty because both trials had different populations and median trial follow-up periods. The EAG considered the adverse event probabilities from DAPA-HF appeared more generalisable to people with heart failure with preserved or mildly reduced ejection fraction. But, it maintained the company's approach of using adverse events probabilities from DELIVER in its base case because the data is available. The committee acknowledged the concerns raised by the EAG but concluded that adverse events probability estimates from DELIVER should be used.

Severity

3.24 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's absolute (3.31) and proportional (0.40) QALY shortfalls were below the cut-offs required for the severity weighting. So, a weighting of 1 was applied in its submission. The committee agreed that it was not appropriate to include a severity modifier in this population.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.25 The company's base-case deterministic ICER was £7,519 per QALY gained (corrected post-clarification questions). The EAG applied the following assumptions in its base case:

- age-adjusted and multiplicative population utilities (see section 3.16)
- hospitalisation for heart failure disutility applied for 2.75 months (see section 3.17)
- non-elective inpatient costs taken from NHS reference costs 2019/2020 and inflated to the 2020/2021 cost year (see section 3.18)
- HRG code cost (EB03E) associated with less severe hospitalisation for heart failure (13-day hospital stay; see section 3.19)
- 6 annual GP visits (see section 3.21)
- removal of amputation as an adverse event in the modelling (see section 3.22)
- removal of dapagliflozin treatment effects from urgent heart failure visit event (see section 3.14)
- removal of dapagliflozin treatment effects from cardiovascular and all-cause survival estimates (see section 3.11).

The EAG's base case with their preferred assumptions, which excluded direct treatment benefit on cardiovascular and all-cause deaths, was £22,972 per QALY gained. Its scenario analyses resulted in ICER estimates of £9,407 (assuming a direct and/or indirect effect of dapagliflozin on all-cause and cardiovascular deaths, and excluding costs associated with non-cardiovascular deaths) to £35,636 per QALY gained (assuming no effect of dapagliflozin on all-cause and cardiovascular deaths). The committee also noted that the EAG base case assumptions and scenarios were all done without refitting the survival risk equations (see section 3.11), and therefore the resulting cost-effectiveness estimates were uncertain. 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 3.13). It did not consider these uncertainties fully resolved with the EAG's approach.

Committee preferred assumptions

3.26 The committee's preferred assumptions were to use:

- age-adjusted and multiplicative population utilities (see section 3.16)
- hospitalisation for heart failure disutility applied for 6 months (see section 3.17)
- HRG code cost (EB03E) associated with less severe hospitalisation for heart failure (13-day hospital stay; see section 3.19)
- 6 annual GP visits (see section 3.21)
- removal of amputation as an adverse event in the modelling (see section 3.22).

The committee considered that there was uncertainty regarding whether it was appropriate to use non-elective inpatient costs taken from NHS reference costs 2019/2020 and inflated to the 2020/2021 cost year, or from NHS reference costs 2020/21, because of the unknown impact of the COVID-19 pandemic (see section 3.18). The committee also considered that it was uncertain whether it was appropriate to assume a treatment effect of dapagliflozin on cardiovascular and all-cause deaths (see section 3.11) or on urgent heart failure visit events (see section 3.14). 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 DELIVER. For example, a comparison of observed outcomes in the trial (such as cardiovascular- and all-cause mortality, and hospitalisations caused by heart failure) versus modelled outcomes. This would need to be survival data specifically produced within the model (as opposed to just the regression analysis), and include the impact of changing KCCQ-TSS health states on survival.

- Scenarios exploring the exclusion of a direct and/or indirect treatment benefit for dapagliflozin on cardiovascular and all-cause deaths, with refitting of the survival model whenever parameters are excluded (for example, a coefficient for treatment effect).

Committee cost-effectiveness estimates

3.27 The committee noted that with its preferred assumptions to modelling survival (see section 3.26), the cost-effectiveness estimates were likely 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

3.28 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 the results from DELIVER did not suggest dapagliflozin 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 dapagliflozin 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

3.29 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. Dapagliflozin 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 dapagliflozin 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 dapagliflozin 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, and noted that NICE's guideline on chronic heart failure in adults: diagnosis and management recommends the measurement of NT-proBNP in people with suspected heart failure, followed by specialist assessment and transthoracic echocardiography. The committee concluded that if dapagliflozin was recommended, it would be started on the advice of a heart failure specialist who can determine the most appropriate treatment.

Conclusion

Recommendation

3.30 The committee concluded that when its preferred assumptions are incorporated, the cost-effectiveness estimates for dapagliflozin are likely higher than what NICE considers a cost-effective use of NHS resources. Therefore, the committee did not recommend dapagliflozin 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.

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Technical leads

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Project manager(s)

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