

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Final appraisal document

**Dapagliflozin for treating chronic heart failure
with reduced ejection fraction**

1 Recommendations

- 1.1 Dapagliflozin is recommended as an option for treating symptomatic chronic heart failure with reduced ejection fraction in adults, only if it is used as an add-on to optimised standard care.
- 1.2 Start treatment of symptomatic heart failure with reduced ejection fraction with dapagliflozin on the advice of a heart failure specialist. Monitoring should be done by the most appropriate healthcare professional.
- 1.3 These recommendations are not intended to affect treatment with dapagliflozin that was started in the NHS before this guidance was published. People having treatment outside these recommendations 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

People with heart failure with reduced ejection fraction may have symptoms that are not controlled well enough despite being on the most appropriate (optimised) treatment. Standard care includes an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin-2 receptor blocker (ARB), with beta blockers and, if tolerated, a mineralocorticoid receptor antagonist (MRA). If symptoms continue, people may be offered sacubitril valsartan, with beta blockers and, if tolerated, MRAs.

A clinical trial compared dapagliflozin as an add-on treatment to standard care (based on an ACE inhibitor, ARB or sacubitril valsartan) with standard care alone. Evidence from the trial shows that dapagliflozin lowers the risk of dying from heart disease, and reduces the likelihood of hospitalisation or an urgent outpatient visit because of heart failure.

There are no trials directly comparing dapagliflozin with sacubitril valsartan. An indirect comparison shows dapagliflozin is likely to be as effective at reducing the risk of death from heart disease.

The cost-effectiveness estimates are within what NICE normally considers an acceptable use of NHS resources. So dapagliflozin is recommended as an add-on to optimised standard care for symptomatic chronic heart failure with reduced ejection fraction.

People whose symptoms continue or worsen on optimised doses of standard care based on ACE inhibitors or ARBs can only start sacubitril valsartan under the supervision of a specialist with access to a multidisciplinary team. So dapagliflozin should only be started on advice from a heart failure specialist.

2 Information about dapagliflozin

Marketing authorisation indication

- 2.1 Dapagliflozin (Forxiga, AstraZeneca) has a marketing authorisation 'for the treatment of symptomatic chronic heart failure with reduced ejection fraction'.

Dosage in the marketing authorisation

- 2.2 The dosage schedule is available in the [summary of product characteristics](#).

Price

- 2.3 The list price of dapagliflozin is £36.59 per 28-tablet pack (excluding VAT; BNF online, accessed November 2020). The annual treatment cost is

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£476.98. Costs may vary in different settings because of negotiated procurement discounts.

3 Committee discussion

The [appraisal committee](#) considered evidence submitted by AstraZeneca, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the [committee papers](#) for full details of the evidence.

The appraisal committee was aware of one issue that was resolved during the technical engagement stage. It agreed that the probabilistic sensitivity analysis provided at technical engagement should inform the comparison with sacubitril valsartan (issue 5, see technical report page 7).

It recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report, table 1, pages 3 to 10), and took these into account in its decision making. It discussed the following issues (issues 1, 2, 3, 4, 6 and 7), which were outstanding after the technical engagement stage.

The condition

People with chronic heart failure with reduced ejection fraction would welcome a new treatment option

3.1 Heart failure with reduced ejection fraction (HFrEF) is a chronic condition that affects survival and quality of life. The patient experts highlighted the psychological effects of a diagnosis and explained that breathlessness, extreme fatigue and fluid accumulation in particular can be debilitating. Clinical expert submissions to NICE confirmed that HFrEF is associated with high rates of death and hospitalisation and that there is an unmet need for new treatment options. Current treatments aim to manage symptoms and stabilise the disease to prevent further decline in quality of life and to keep people alive longer. The committee heard from clinical experts that despite optimising therapies, many people still have

symptoms, including breathlessness. The patient experts said that they would welcome a new option, especially if it could be used early in the treatment pathway. The committee concluded that there is an unmet need for a new treatment option for symptomatic HFrEF and that patients and healthcare professionals would welcome a new treatment option.

The treatment pathway

If symptoms worsen or continue on optimised standard care specialist advice is needed

3.2 [NICE's guideline on chronic heart failure in adults: diagnosis and management](#) recommends that a specialist heart failure multidisciplinary team work collaboratively with the primary care team. It recommends that the specialist multidisciplinary team diagnose heart failure, optimise treatment and manage heart failure not responding to treatment. Recommended drug treatments for newly diagnosed HFrEF include diuretics for congestive symptoms and fluid retention, and an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin-II receptor blocker (ARB) when an ACE inhibitor is not tolerated, aiming for maximum tolerated doses. A beta blocker and a mineralocorticoid receptor antagonist (MRA) should also be offered if appropriate and tolerated. The clinical experts said that current clinical practice is to get specialist advice, or refer a patient to specialist care, if symptoms worsen or continue after optimising standard care with ACE inhibitors or ARBs, beta blockers and, if tolerated, MRAs (referred to in this guidance as standard care based on ACE inhibitors or ARBs). NICE's guidance says that subsequent treatment with sacubitril valsartan or ivabradine should be started under the supervision of a specialist with access to a multidisciplinary team (see [NICE's guidance on sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction](#) and [NICE's guidance on ivabradine for treating chronic heart failure](#)). Treatment with hydralazine plus nitrate or digoxin also requires specialist advice. The clinical experts said that specialist care might include heart failure teams based in the

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community or GPs with a special interest in heart failure. The committee concluded that current clinical practice involved specialist advice or referral to specialist care if symptoms worsen or continue on optimised standard care based on ACE inhibitors or ARBs.

Clinical evidence

The DAPA-HF trial is the key trial for dapagliflozin and is broadly generalisable to NHS clinical practice

3.3 DAPA-HF was a double-blind randomised clinical trial comparing dapagliflozin (a sodium-glucose cotransporter-2 inhibitor) plus standard care with placebo plus standard care. Standard care was defined by the company as:

- standard care based on ACE inhibitors or ARBs, or
- sacubitril valsartan, plus beta blockers, and, if tolerated, MRAs (referred to in this guidance as standard care based on sacubitril valsartan).

People in the trial had HFrEF defined by an ejection fraction of 40% or less who despite being 'optimally treated with pharmacological and/or device therapy' remain symptomatic. Symptomatic HFrEF was defined as New York Heart Association (NYHA) functional class II to IV present for at least 2 months. Eleven percent of people in the trial had sacubitril valsartan at baseline. Nineteen per cent of patients had digoxin and 5% had ivabradine. Thirty-eight per cent of patients had co-existing atrial fibrillation, 42% had diabetes and 41% had chronic kidney disease. The clinical experts said that the trial findings were generalisable to NHS clinical practice but highlighted several differences between the population in DAPA-HF and the population in the NHS:

- The average age in the full population was 66, which is younger than in the NHS where the average age at diagnosis is 77.
- The proportion of men was higher in the trial than in the NHS.

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- Not all people in the trial were taking NICE guideline-recommended doses of standard care.
- More people were taking diuretics in the trial than in the NHS.

The ERG said that the characteristics of people in DAPA-HF, which is a multinational trial, may not reflect that of the population in the NHS. It noted the differences in healthcare systems in different countries. The ERG preferred the European subgroup of the trial, which had an older population (mean age 68) with more severe disease whose background therapies better reflected those in the NHS. However, the European subgroup was over 99% white and was only 45% of the full DAPA-HF population. The clinical experts explained that the relative clinical effectiveness results were not expected to change as a result of these differences in baseline characteristics. The committee recognised that the absolute risk of complications might differ between the European subgroup and the patients from the rest of the world. It also recognised that larger populations are associated with less uncertainty. The committee concluded that data from the overall DAPA-HF population were acceptable for decision making, and it was therefore appropriate to use these for the clinical effectiveness analyses.

The DAPA-HF trial is generalisable to people whose standard care has been optimised

- 3.4 People in the DAPA-HF trial were clinically stable and optimised on heart failure therapies according to local guidelines. The trial protocol inclusion criteria listed that therapy should have been individually optimised and stable for 4 weeks or more. It also noted that participants should 'be treated with a diuretic regimen aimed at achieving optimal fluid/volume status for that individual'. The clinical experts confirmed that if dapagliflozin were available, clinicians would start dapagliflozin only in people stable on standard heart failure treatments available in the NHS. The company confirmed that this included loop diuretics, which are used

together with ACE inhibitors and ARBs based on patient symptoms and clinical presentation. The committee agreed that, in line with the clinical evidence, in the NHS dapagliflozin would be offered to people taking optimised doses of standard care based either on an ACE inhibitor or ARB, or on sacubitril valsartan, and that the DAPA-HF trial results are generalisable to people whose standard care has been optimised.

Dapagliflozin plus standard care compared with placebo plus standard care is clinically effective

3.5 The primary efficacy outcome in the DAPA-HF trial was a composite of cardiovascular death, and hospitalisation for heart failure or an urgent heart failure visit. Intention-to-treat analyses showed that dapagliflozin plus standard care reduced the incidence of the primary endpoint of composite cardiovascular events by 26% compared with placebo plus standard care (hazard ratio 0.74, 95% confidence interval 0.65 to 0.85; $p < 0.001$). It also reduced the incidence of all the individual components of the composite endpoint. Secondary endpoints included change in Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS) at 8 months and death from any cause. Among people randomised to dapagliflozin, 12% of people died compared with 14% of people randomised to placebo. Cox survival modelling estimated a hazard ratio of 0.83 (95% confidence interval 0.71 to 0.97) in favour of dapagliflozin. The committee concluded that dapagliflozin is clinically effective compared with placebo and reduces the risk of cardiovascular events and all-cause mortality when added to standard care.

Risk factors for adverse effects should be identified, and increased monitoring may be needed with dapagliflozin

3.6 The frequency and type of most adverse events were broadly similar for people on the dapagliflozin and placebo arms of DAPA-HF. However, in the DAPA-HF trial, more people on dapagliflozin had diabetic ketoacidosis and volume depletion, and fewer people had acute kidney injury. The

marketing authorisation for dapagliflozin says: 'Before initiating dapagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered.' Dapagliflozin has a separate marketing authorisation as a glucose-lowering agent for type 1 and type 2 diabetes, but the marketing authorisation prohibits prescribing dapagliflozin to people with type 1 diabetes at the dose used for HFrEF. One clinical expert said that additional kidney function monitoring may be needed for dapagliflozin based on its mechanism of action. The marketing authorisation for dapagliflozin also says that for people treated with dapagliflozin for heart failure and type 2 diabetes, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia. The committee was aware that at times increased monitoring may be needed in people taking dapagliflozin for heart failure, for example, with intercurrent illness to monitor for volume depletion. Non-severe genital infections, a common adverse effect for dapagliflozin in diabetes, were not collected in the DAPA-HF trial but the protocol was amended to collect more severe genital infections. The company included incidence rates for genital infections in the cost-effectiveness modelling taken from the DECLARE-TIMI 58 trial, a placebo-controlled cardiovascular outcomes safety trial in type 2 diabetes. The committee concluded that the safety data from the DAPA-HF trial with the genital infections data from the DECLARE-TIMI 58 trial accurately capture the adverse effects of dapagliflozin, but that risk factors for adverse effects should be identified and increased monitoring may be needed.

Comparators

ACE inhibitors, ARBs, diuretics, beta-blockers and MRAs are not direct comparators alone, but are comparators when used in combination as standard care

3.7 The committee heard from a patient expert that they wished dapagliflozin to be used as early as possible in treating heart failure (see section 3.1).

But the committee recalled its earlier conclusion, based on the trial evidence presented, that dapagliflozin would be used after standard care is optimised. For this reason, the committee concluded that optimised standard care, rather than the individual components, reflected what patients would otherwise be offered. It agreed that ACE inhibitors, ARBs, diuretics, beta blockers and MRAs were not direct comparators alone but are comparators when used in combination as standard care.

Ivabradine, digoxin and hydralazine with nitrate are not relevant comparators

3.8 [NICE's guideline on chronic heart failure in adults: diagnosis and management](#) recommends sacubitril valsartan, ivabradine and hydralazine with nitrate or digoxin as specialist treatments for HFrEF. The final scope for this guidance did not include ivabradine, digoxin and hydralazine with nitrate as relevant comparators for dapagliflozin. The clinical experts explained that these drugs are rarely prescribed in clinical practice for HFrEF. They said that ivabradine is primarily a heart-rate-lowering medicine for people with left ventricular systolic dysfunction who are in sinus rhythm and have a resting heart rate of over 75 beats per minute. One clinical expert noted that hydralazine with nitrate is used in people with poor kidney function or for whom ACE inhibitors are not suitable. A clinical expert said that digoxin is used in atrial fibrillation and in worsening or severe heart failure with sinus rhythm when reduced kidney function means no other treatments are an option. A clinical expert explained that hydralazine with nitrate and digoxin are generally used in different populations and would not be relevant at this point in the pathway. The company provided pharmacoepidemiologic data from the Clinical Practice Research Datalink which suggests that around 2%, 1% and 11% of people with heart failure have ivabradine, hydralazine with nitrate and digoxin in NHS practice, respectively. However, the committee recognised that these data included people with preserved ejection fraction and that all 3 technologies are licensed for other indications, so

the proportion of people taking these medicines in England to treat HFrEF was likely to be lower. The committee concluded that ivabradine, digoxin and hydralazine with nitrate are not relevant comparators for dapagliflozin.

Sacubitril valsartan is an appropriate comparator

3.9 The clinical experts explained that currently they would consider sacubitril valsartan as an option for people whose symptoms continue on optimised standard care based on ACE inhibitors or ARBs. If dapagliflozin were available, the clinical experts noted that specialist teams considering sacubitril valsartan would take into account which treatment was more appropriate based on a person's symptoms and comorbidities. The committee agreed that sacubitril valsartan was an appropriate comparator.

Optimised standard care based on sacubitril valsartan is also an appropriate comparator

3.10 The clinical experts explained that it was likely that for many people symptoms would continue on sacubitril valsartan, so it was reasonable to consider dapagliflozin as an add-on to standard care at this point in the pathway. The committee concluded that, for people who remain symptomatic on sacubitril valsartan, standard care based on sacubitril valsartan is the relevant comparator.

Optimised standard care based on ACE inhibitors or ARBs is the appropriate comparator for people who cannot take sacubitril valsartan

3.11 The committee then considered a population proposed by the company who could not take sacubitril valsartan but could take dapagliflozin. One clinical expert confirmed that they would include people with hypotension or with poor kidney function in the population that cannot have sacubitril valsartan. However, for both sacubitril valsartan and dapagliflozin, there is very limited clinical experience in people with severe kidney impairment (estimated glomerular filtration rate [GFR] less than 30 ml/min/1.73 m²).

The committee noted that people with a left ventricular ejection fraction

between 36% and 40% would not be offered sacubitril valsartan, in line with NICE guidance, but could be offered dapagliflozin. The GP committee members said that they would not determine who could and could not take sacubitril valsartan. They said they would refer anyone who continued to have symptoms despite being optimised on standard care based on ACE inhibitors or ARBs to heart failure specialist care. The committee agreed that members of specialist heart failure teams are able to define and identify people who cannot or should not take sacubitril valsartan. It concluded that the appropriate comparator for these people is optimised standard care based on ACE inhibitors or ARBs (see section 3.7).

Indirect treatment comparison

The Bucher method is appropriate for an indirect comparison of dapagliflozin with sacubitril valsartan

3.12 There were no trials directly comparing dapagliflozin with sacubitril valsartan. To estimate the relative efficacy of dapagliflozin plus standard care based on ACE inhibitors with sacubitril valsartan with beta blockers and, if tolerated, MRAs, the company used a matching-adjusted indirect comparison. This adjusted patient-level data from people in DAPA-HF to match study-level baseline patient characteristics from PARADIGM-HF, a randomised controlled trial comparing sacubitril valsartan with enalapril (an ACE inhibitor). The ERG explained that the results of the matching-adjusted indirect comparison were uncertain because the company excluded a large proportion of the DAPA-HF population when adjusting it to match the baseline characteristics of participants in the PARADIGM-HF trial. The ERG said that the company had not justified why it had chosen a matching-adjusted indirect comparison. The company also presented an analysis using the alternative Bucher method, which compares treatments without matching baseline characteristics across trials and used the whole DAPA-HF population. The ERG noted that results using both methods were similar, which suggested it was unlikely that the baseline

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characteristics of participants in the PARADIGM-HF and DAPA-HF trial were substantially different and required matching. Because of this, the ERG preferred the Bucher method, which gives more precise estimates, for its analyses. The committee concluded that results from the matching-adjusted indirect comparison were associated with higher uncertainty and that the Bucher method should be used to compare effectiveness of dapagliflozin with sacubitril valsartan.

Dapagliflozin may be more effective than sacubitril valsartan, but the results are uncertain

3.13 The primary endpoint in the indirect comparison was time to first hospitalisation for heart failure or cardiovascular death because these data were available from both the DAPA-HF and the PARADIGM-HF trial. The results from the indirect treatment comparison indicated that dapagliflozin was more effective than sacubitril valsartan at improving time to cardiovascular events. However, the committee noted that the results were uncertain and included the possibility of no benefit for dapagliflozin compared with sacubitril valsartan (a relative risk of 1.0). The committee was aware that the company originally modelled dapagliflozin as equally effective as sacubitril valsartan in its submission. The committee concluded it would consider both the relative effectiveness results from the Bucher method and the results from assuming equal effectiveness with sacubitril valsartan in its decision making.

The company's economic model

The company's model is appropriate for decision making

3.14 The company modelled cost effectiveness using a Markov model with 5 states (4 based on symptom severity plus 1 for death). It captured disease severity using the KCCQ-TSS, which is a disease-specific measure of quality of life. People transitioned through quartiles based on KCCQ-TSS (0 to 100, with high scores denoting lower symptom burden) and a specific utility and cost associated with each state. The ERG noted that

cut offs for the quartiles chosen by the company to measure KCCQ-TSS in the model were arbitrary. But it said it expected that using other cut offs or approaches to grouping would minimally affect the cost-effectiveness results. The company also modelled hospitalisation for heart failure, urgent heart failure visits and adverse events based on the incidence in each quartile, and stratified people by whether they had type 2 diabetes at baseline. The model included a treatment effect (relative effectiveness from DAPA-HF and Bucher indirect treatment comparison) using survival equations. The committee concluded that the company's model structure was appropriate for decision making.

The KCCQ tool is a reasonable way to measure disease severity

3.15 The company's model structure differed from those used in [NICE's guidance on sacubitril valsartan](#) and [ivabradine](#). These used a 2-state dead and alive Markov model and indirectly measured disease severity using the NYHA classification (in survival equations and baseline characteristics). The company said it considered that scores from patient questionnaires, like the KCCQ tool, were more accurate for measuring symptom severity than the NYHA classification, which was based on healthcare professionals' assessments. The clinical experts confirmed that, although NYHA classification is more commonly used in clinical practice, it is more subjective and less sensitive to changes in patient symptoms than the KCCQ tool. The results of a subgroup analysis from DAPA-HF showed a difference in treatment effect by NYHA classification. The company explained that there was no plausible biological explanation for this finding and results of subgroup analyses in other markers of disease severity (such as prior hospitalisation for heart failure and left ventricular ejection fraction) did not find a difference. In response to technical engagement, the company presented data on health state occupancy over time using the NYHA class for disease severity. This placed most people from the DAPA-HF control arm in the NYHA class I or II health state (zero to mild symptoms) over the model time horizon. One

clinical expert confirmed that this did not reflect the chronic nature of HFrEF. The company explained that health state occupancy using KCCQ-TSS better aligned with the expected symptom changes for standard care: initial improvement for 4 to 8 months then stabilisation. The company also said that few people were NYHA class I or IV at baseline so the transition probabilities in these health states would be uncertain. The committee concluded that the KCCQ tool is a reasonable way to classify disease severity and is appropriate for decision making.

Survival extrapolations for cardiovascular and all-cause mortality

A Gompertz distribution produces the most plausible survival extrapolations, but the distribution used has limited impact on cost-effectiveness results

3.16 The mortality data from the DAPA-HF trial were relatively immature because only 12% and 14% of people had died in the dapagliflozin and placebo arms respectively (median follow up was 18 months). The company used a Weibull distribution to extrapolate cardiovascular and all-cause mortality beyond the end of the trial for the entire duration of the model in its base-case analysis. A clinical expert said that the Weibull curve predicted survival estimates that were aligned with those in NICE's guidance on sacubitril valsartan and their own audit. The ERG confirmed that, based on the observed data, it was plausible to use the Weibull distribution and to assume proportional hazards. However, Taylor et al.'s 2019 study of trends in overall heart failure survival in the UK (for reduced and preserved ejection fraction) predicted fewer people would be alive at 1 year, 5 years and 10 years than estimated by the Weibull distribution. The committee noted these data aligned better with the survival estimates predicted using the Gompertz curve, although they may still overestimate survival given the poor prognosis for HFrEF. The company did not validate its survival estimates using epidemiological data. The committee noted that the incremental proportional hazards and treatment effect

appeared to be maintained across the different extrapolation methods. Because of this, the choice of distribution to extrapolate survival had little impact on the cost effectiveness of dapagliflozin. The committee concluded that extrapolating survival with a Gompertz distribution is the most plausible for decision making, but that the distribution used has limited impact on cost-effectiveness results.

Treatment waning

Excluding waning of the treatment effect from the model is appropriate

3.17 The company modelled the relative survival benefit for dapagliflozin plus standard care as being maintained at the same level for the rest of the person's life. It justified this by noting that the DAPA-HF trial had no stopping rule for dapagliflozin and NICE's guidance on sacubitril valsartan assumed no waning of effect. Also, the treatment effect for dapagliflozin was stable in DAPA-HF and the DECLARE-TIMI 58 trial, the latter of which had a median follow up of 4.2 years. The committee questioned whether it was possible that treatment effect may not be continued over a lifetime, as seen for some diuretic treatments. It noted there was no evidence for or against treatment waning in the long term. Clinical experts and stakeholders confirmed that treatment with dapagliflozin would likely be lifelong. Because the maximum follow up in the DAPA-HF trial was 2.3 years, the committee considered the company's scenarios in which the treatment effect of dapagliflozin stopped at 3 years, 5 years and 10 years from starting treatment. However, it noted that cost-effectiveness results were robust to these scenarios. The committee concluded that it is appropriate that the model does not include waning of the treatment effect, and that incorporating this assumption has limited impact on the cost-effectiveness results.

Utilities

Utility values from the DAPA-HF trial and the literature should both be considered in decision making

3.18 In its initial base case, the company used utilities derived directly from EQ-5D-5L questionnaires collected in the DAPA-HF trial. The company mapped the EQ-5D-5L data to EQ-5D-3L to estimate mean utility values for all health states, in line with [NICE's methods guide](#). The ERG noted that the company's utility value for KCCQ-TSS quartile 4 (people with the lowest reported symptom burden) was 0.833. The committee noted that this was higher than the 0.774 utility value for the general population aged 60 to 69 calculated by Sullivan et al. (2011). The clinical experts pointed out that people with heart failure are unlikely to have a better quality of life than the general public for the same age range. For this reason, the ERG preferred a scenario that used the utility value from Sullivan et al. for KCCQ-TSS quartile 4 and applied the relative differences between quartiles that was observed in the DAPA-HF study to calculate utilities for quartiles 1 to 3. The committee noted that utility values taken directly from the clinical trial are often preferred but considered the high values from the unadjusted DAPA-HF utilities to lack face validity. It concluded that it would consider utility values from the DAPA-HF trial and the literature in its decision making.

Costs

Costs used in the company's model are appropriate for decision making

3.19 The company's model included costs of treatment with dapagliflozin and sacubitril valsartan at list price, but the committee was aware that the cost of sacubitril valsartan may vary in different settings due to negotiated procurement discounts. The company assumed that treatment costs accrued over a person's lifetime until that person stopped treatment because of adverse events or by choice. The committee was aware that because standard care costs were included in both arms of the DAPA-HF

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trial they had limited impact on the overall cost-effectiveness results. Costs were associated with hospitalisation for heart failure, an urgent heart failure visit, death from heart disease, and having type 2 diabetes at baseline. The company included costs for adverse events including hypoglycaemia, volume depletion, fractures, kidney adverse events and diabetic ketoacidosis as well as genital and urinary tract infections. The committee concluded that the costs used in the company's model were appropriate for decision making.

Cost-effectiveness estimates

Dapagliflozin dominates sacubitril valsartan in all scenarios

3.20 Dapagliflozin dominated sacubitril valsartan in the company and ERG's base cases (that is, it was less costly and at least equally effective). This was true for all scenarios, including when the company used alternative methods of indirect comparison or if equal clinical effectiveness between dapagliflozin and sacubitril valsartan was assumed. Exact costs for the comparison with sacubitril valsartan are not reported because of varying procurement discounts associated with sacubitril valsartan in different settings. The committee concluded that dapagliflozin added on to optimised standard care based on ACE inhibitors or ARBs is less costly and at least equally effective as optimised sacubitril valsartan with beta blockers and, if tolerated, MRAs.

Dapagliflozin plus standard care is cost effective as an add-on to optimised standard care

3.21 The committee first considered the population taking dapagliflozin as an add-on to optimised standard care based on ACE inhibitors or ARBs. The company's base-case incremental cost-effectiveness ratio (ICER) (updated at technical engagement) was £6,939 per quality-adjusted life year (QALY) gained. The ICERs for company scenarios ranged from £5,435 to £17,087 per QALY gained. The ERG's preferred assumptions, which used baseline characteristics and the treatment effect from the

European subgroup, increased the ICER to around £18,000 per QALY gained. However, the committee recalled that it did not consider the European subgroup the most appropriate for decision making (see section 3.3). The committee agreed that its preferred assumptions to compare dapagliflozin added to optimised standard care (based on ACE inhibitors or ARBs) with optimised standard care (based on ACE inhibitors or ARBs) without dapagliflozin included:

- the Gompertz distribution to calculate overall and cardiovascular mortality
- the whole DAPA-HF population for baseline characteristics and treatment effect
- no waning of treatment effect
- utility values from the DAPA-HF trial and the literature.

Using the above assumptions with utility values from the DAPA-HF trial, the committee's preferred ICER for dapagliflozin was £7,264 per QALY gained as an add-on to optimised standard care based on ACE inhibitors or ARBs. The committee understood that the ICER would be higher if utility values from the literature were used but that this increase would be minimal.

The committee then considered the population taking dapagliflozin as an add-on to optimised standard care based on sacubitril valsartan. The cost-effectiveness results are not reported here because of varying procurement discounts associated with sacubitril valsartan in different settings. However, the committee noted that its preferred ICER for this population would be under £10,000 per QALY gained. It concluded that the most plausible ICERs were within what NICE normally considers to be a cost-effective use of NHS resources and that dapagliflozin is cost effective when compared with optimised standard care based on ACE inhibitors or ARBs, or optimised standard care based on sacubitril valsartan.

Other factors

Dapagliflozin is innovative and the benefits for people with diabetes and heart failure may not be fully captured in the model

3.22 The committee recalled that people with HFrEF have a poor prognosis and that there is an unmet need for treatment options (see section 3.1). The committee noted that it is the first drug of its class to gain regulatory approval for use in heart failure. It also considered that dapagliflozin has a marketing authorisation for the treatment of glycaemic control in people with diabetes, who comprised a large proportion of the DAPA-HF trial (see section 3.3). The committee recalled that the company had not included additional benefits (for example, prevention of diabetic eye disease) associated with improved glycaemic control for diabetes. The committee concluded that dapagliflozin is innovative and is a step-change in the treatment of HFrEF, and that the benefits for people who also have diabetes may not be fully captured in the model.

A heart failure specialist should advise on starting dapagliflozin

3.23 The committee recalled its earlier conclusion that current clinical practice involved specialist advice or referral to specialist care if symptoms worsen or continue on optimised doses of standard care based on ACE inhibitors or ARBs, to determine the appropriate next treatment. It recalled that regulatory advice for dapagliflozin as a treatment for heart failure is to identify people at high risk of adverse effects before starting treatment (see section 3.6). The company positioned dapagliflozin as an add-on treatment to standard care, highlighting that dapagliflozin could be started before consulting specialist care while people awaited referral. The GPs on the committee said they would not start dapagliflozin without consulting a specialist or heart failure team. The patient expert said that primary care clinicians are familiar with prescribing the drug for type 2 diabetes. However, the committee was aware that the population in the current marketing authorisation for dapagliflozin for heart failure differed from the

population for dapagliflozin for diabetes and included people with worse kidney function (with estimated GFR values down to 30 ml/min/1.73m²). The committee noted that GPs would not be familiar in treating these people with dapagliflozin for diabetes. One clinical expert said that everyone with a new diagnosis of heart failure would see a specialist to start and manage treatment, so people who could have dapagliflozin would already be known to specialist care. The committee concluded that dapagliflozin should be started on advice from a heart failure specialist who can determine the most appropriate treatment.

Monitoring should be done by the most appropriate healthcare professional

3.24 [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. [NICE's guidance for sacubitril valsartan](#) says that monitoring should be carried out by a heart failure specialist or in primary care by the most appropriate team member. A clinical expert said that people who were taking dapagliflozin for heart failure who also had diabetes might need adjustments in their diabetes medication for safety reasons (see section 3.6). The committee recalled its conclusion that risk factors should be identified and some increased monitoring may be needed for treating heart failure with dapagliflozin. It concluded that monitoring of people who have dapagliflozin for heart failure should be done by the most appropriate healthcare professional from a specialist heart failure multidisciplinary team or primary care team.

No equalities considerations were identified for dapagliflozin

3.25 The committee recalled that dapagliflozin is currently offered to people with diabetes in primary and in secondary care. A patient expert explained that, if dapagliflozin were limited to specialist care for heart failure, people with type 2 diabetes would have access to it in primary care, but people

who had HFrEF without diabetes would not. The committee considered that the population who had HFrEF were likely to be older and have worse kidney function than people with diabetes alone. The committee recalled standard clinical practice is for a heart failure specialist and a multidisciplinary team to determine the most appropriate second-line treatment to offer. It noted that specialist advice could be given to a primary care healthcare professional, so people would not need to visit a hospital to start dapagliflozin. The committee noted its recommendation applied to all people included in the dapagliflozin for HFrEF marketing authorisation and not only those with comorbid diabetes. It therefore did not consider this an equalities issue.

Conclusion

Dapagliflozin is recommended for use in the NHS

3.26 The committee agreed that the most plausible ICERs for dapagliflozin compared with all relevant comparators were within what NICE normally considers to be an acceptable use of NHS resources. It therefore concluded that it could recommend dapagliflozin for routine commissioning as an option to treat symptomatic chronic HFrEF as an add-on in people who are already taking optimised standard care based on an ACE inhibitor or ARB, or on sacubitril valsartan.

4 Implementation

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

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE

technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

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

5 Review of guidance

- 5.1 The guidance on this technology will be considered for review 3 years after publication. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler
Chair, appraisal committee
December 2020

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee B](#).

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

The [minutes of each appraisal committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

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

Emma Douch

Technical lead

Lorna Dunning

Technical adviser

Joanne Ekeledo

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