NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Dapagliflozin for treating chronic kidney disease

1   Recommendations

1.1   Dapagliflozin is recommended as an option for treating chronic kidney disease (CKD) in adults. It is recommended only if:

- it is an add-on to optimised standard care including the highest tolerated licensed dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), unless these are contraindicated, and
- people have an estimated glomerular filtration rate (eGFR) of 25 ml/min/1.73 m^2 to 75 ml/min/1.73 m^2 at the start of treatment and:
  - have type 2 diabetes or
  - have a urine albumin-to-creatinine ratio (uACR) of 22.6 mg/mmol or more.

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

Management of CKD aims to slow disease progression. Standard care is lifestyle and dietary changes, and usually ACE inhibitors or ARBs. Dapagliflozin is an oral treatment for CKD. The company proposes that dapagliflozin would be used as an

add-on to optimised standard care with ACE inhibitors or ARBs, which is narrower than its marketing authorisation.

Clinical trial evidence suggests that dapagliflozin plus standard care is more effective than standard care alone. The main clinical trial only included people with an eGFR of 25 ml/min/1.73 m^2 to 75 ml/min/1.73 m^2 and a uACR of 22.6 mg/mmol to 565 mg/mmol. Evidence is available for dapagliflozin from a different clinical trial for people with CKD and type 2 diabetes and with a uACR of less than 22.6 mg/mmol. There is no clinical trial evidence available for dapagliflozin in people with CKD without type 2 diabetes and with a uACR of less than 22.6 mg/mmol.

For the groups for which there is good enough clinical evidence, the cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, dapagliflozin is recommended for these groups as an add-on to optimised standard care including ACE inhibitors or ARBs.

2   Information about dapagliflozin

Marketing authorisation indication

2.1   Dapagliflozin (Forxiga, AstraZeneca) is indicated for 'treating chronic kidney disease (CKD) in adults'.

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 for a 28-pack of 10 mg tablets, giving a yearly cost of £477.30. 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) and responses from stakeholders. See the [committee papers](#) for full details of the evidence.

The appraisal committee recognised that there were remaining areas of uncertainty associated with the analyses presented and took these into account in its decision making. It discussed the following issues, which were outstanding after the technical engagement stage:

- the uncertainty around the target patient population and the effectiveness of dapagliflozin in people excluded from the DAPA-CKD trial (issue 1, see ERG report page 12)
- concerns about the company's overall modelling approach and overall survival predictions (issue 2, see ERG report page 13).

The condition

Chronic kidney disease can have substantial effects on quality of life

3.1 Chronic kidney disease (CKD) is a complex progressive disorder with loss of nephrons causing kidney function to decline over time. This can eventually lead to end-stage renal disease and death. CKD happens because of systemic disease affecting the kidney, such as type 2 diabetes, hypertension or cardiovascular disease, or from primary kidney disease such as glomerulonephritis. Conditions such as type 2 diabetes, hypertension and cardiovascular disease can also be caused by CKD. CKD varies in severity and the [NICE guideline for chronic kidney disease: assessment and management](#) (NG203) recommends classifying CKD in adults using a combination of glomerular filtration rate (GFR) and albumin-to-creatinine ratio (ACR). GFR is a measure of kidney function, estimated using a creatinine blood test (eGFR). eGFR is categorised from G1 (eGFR of more than 90 ml/min/1.73 m^2), defined as no reduction in kidney function, to G5 (eGFR of less than 15 ml/min/1.73 m^2), defined as kidney

failure. ACR is a marker of kidney damage, measured using a urine sample (uACR). uACR is categorised from A1 (uACR of less than 3 mg/mmol), defined as normal or mild damage, to A3 (uACR of more than 30 mg/mmol), defined as severe damage. Around 1.9 million adults in the UK have CKD with an eGFR category of G3a to G5, and it is likely there are many more undiagnosed. Patient experts highlighted that CKD can have huge implications on a person's quality of life. They explained that CKD affects mental health and emotional wellbeing, capacity to stay in work and the ability to maintain relationships. People with CKD must spend a significant amount of time in hospital, especially when having dialysis treatment. The committee noted the additional support people need with daily activities and treatment, and the impact of this on carers. It concluded that CKD represents a significant burden for people and can substantially affect both physical and psychological aspects of quality of life.

Treatment pathway and comparator

There is an unmet need for more effective treatments for CKD and a new treatment option would be welcomed

3.2 The patient and clinical experts highlighted that CKD is incurable with limited pharmacological options for delaying progression. The clinical experts explained that the main aims of treatment are to prevent disease progression and reduce cardiovascular morbidity and mortality. They explained that the current treatment pathway for CKD is not particularly well defined, and the evidence is rapidly changing. However, there is a general alignment of treatment practice with NG203. The guideline recommends lifestyle advice including dietary interventions for adults with CKD. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) are standard pharmacological management for CKD, but these only slow disease progression. Patient experts reiterated that preventing disease progression and delaying the need for a kidney

transplant are particularly important for people with CKD. The committee noted that with current best practice CKD can often still progress to end-stage renal disease. It concluded that there is an unmet need for more effective therapies for treating CKD, and that patients and clinicians would welcome a new treatment option.

Dapagliflozin would be used as an add-on to optimised standard care, including an ACE inhibitor or ARB

3.3   In its original submission the company positioned dapagliflozin for people having optimised standard care, which may or may not have included an ACE inhibitor or ARB. The ERG highlighted that this was inconsistent with the main source of clinical evidence for dapagliflozin in treating CKD, the DAPA-CKD trial (see section 3.7). This is because 97% of people in DAPA-CKD were either having an optimised ACE inhibitor or ARB. In response to technical engagement the company updated its positioning to people who were having an optimised ACE inhibitor or ARB. The committee was aware that NICE's guideline for type 2 diabetes in adults: management (NG28) recommends sodium-glucose cotransporter-2 (SGLT2) inhibitors for people with CKD and type 2 diabetes who are having an optimised ACE inhibitor or ARB. It is considered best practice to offer an ACE inhibitor or ARB at an optimised dose before prescribing an SGLT2 inhibitor. The clinical experts agreed that although dapagliflozin would likely have some benefit for people not having an ACE inhibitor or ARB, it should be used as an add-on to these treatments. They explained that most people would already be having an ACE inhibitor or ARB and would likely continue having these until needing dialysis. The committee concluded that dapagliflozin would be used as an add-on to optimised standard care, including an ACE inhibitor or ARB at the highest tolerated licensed dose, unless these are contraindicated.

Standard care is an appropriate comparator for dapagliflozin

3.4   In its submission the company compared dapagliflozin plus standard care with standard care alone. The company represented standard care using the placebo arm of DAPA-CKD (see section 3.7). This comprised of background therapies including ACE inhibitors or ARBs, statins and antiplatelets. The ERG agreed with the company's description of how CKD is currently managed in the UK. The committee concluded that standard care is an appropriate comparator for dapagliflozin.

Canagliflozin is a relevant comparator in people with diabetic kidney disease

3.5   Canagliflozin is another SGLT2 inhibitor with a marketing authorisation for type 2 diabetes. The company did not consider canagliflozin a relevant comparator for dapagliflozin in CKD, because it noted that canagliflozin is not widely used for treating CKD with type 2 diabetes in the UK. However, the company did an indirect treatment comparison of dapagliflozin and canagliflozin in people with CKD and type 2 diabetes (see section 3.11). The clinical experts noted that canagliflozin is being increasingly used by nephrologists, but acknowledged that the guidelines supporting the use of SGLT2 inhibitors in people with CKD were relatively new. NG28 recommends offering an SGLT2 inhibitor to adults with CKD and type 2 diabetes, in addition to an ACE inhibitor or ARB, if their ACR is more than 30 mg/mmol and they meet the criteria in the marketing authorisation. NG28 also recommends considering an SGLT2 inhibitor for adults with CKD and type 2 diabetes, in addition to an ACE inhibitor or ARB, if their ACR is between 3 mg/mmol and 30 mg/mmol and they meet the criteria in the marketing authorisation. The committee noted that the comparator in the NICE scope was established clinical management without dapagliflozin. The committee considered that, since canagliflozin was recommended in NG28 and is being used to some extent in clinical practice, it represents established clinical practice for people with CKD and type 2 diabetes. In response to consultation the company reiterated

that the uptake of canagliflozin has been slow in UK clinical practice for people having treatment for CKD. It also noted that canagliflozin has a marketing authorisation for treating diabetic kidney disease (CKD caused by type 2 diabetes). This is a subgroup of people with CKD and type 2 diabetes. The ERG explained that it is reasonable to include canagliflozin as a comparator for the subgroup of people with comorbid type 2 diabetes, when the licensed indications for both treatments overlap. The committee concluded that canagliflozin is a relevant comparator in people with diabetic kidney disease.

It is appropriate to make recommendations for dapagliflozin based on uACR levels

3.6   In its updated economic model, the company split the population into subgroups based on uACR level and type 2 diabetes status (see section 3.14). NG203 recommends measuring proteinuria with uACR in adults with an eGFR of less than 60 ml/min/1.73 m^2, or in adults with an eGFR of more than 60 ml/min/1.73 m^2 if there is a strong suspicion of CKD. The clinical experts explained that uACR testing is not done consistently in clinical practice. They noted that although the test is simple to do, there is some hesitancy about doing urine tests, particularly when there may be a delay before getting the results. The committee heard from a patient expert who explained that they would not hesitate to provide a urine sample, particularly if this ensured they had the best treatment. The clinical experts added that urine protein-to-creatinine ratio (uPCR) tests are widely done, but it is difficult to map the results of uACR and uPCR tests to each other accurately. They explained that in their experience, uACR is no more difficult to measure than uPCR, but would need a change in practice. During consultation, the company highlighted that making recommendations based on uACR levels would risk people not having access to dapagliflozin because of a lack of testing, particularly those without type 2 diabetes. A consultee also advised that the prevalence of proteinuria testing differs by age and ethnicity. The

committee acknowledged that uACR testing is not currently implemented consistently in the NHS. If this did not change, limiting dapagliflozin to subgroups based on uACR levels may negatively affect patient access. However, uACR testing is easy to do, has value in identifying people with CKD who are likely to benefit from dapagliflozin, and is recommended in NG203. Therefore the committee concluded that the current low levels of uACR testing should not prevent it from being included as a criterion in recommendations for dapagliflozin.

Clinical-effectiveness evidence

DAPA-CKD suggests that dapagliflozin is more effective than standard care, but the evidence does not cover the full marketing authorisation

3.7   The main clinical evidence for dapagliflozin in the company submission came from DAPA-CKD. This was a randomised, double-blind trial in adults with CKD, with or without type 2 diabetes. DAPA-CKD compared dapagliflozin plus standard care (n=2,152) with placebo plus standard care (n=2,152) over a median follow-up period of 2.4 years. DAPA-CKD included people with an eGFR of 25 ml/min/1.73 m^2 to 75 ml/min/1.73 m^2 and a uACR of 22.6 mg/mmol to 565 mg/mmol. People's disease had to be stable on a maximum tolerated dose of an ACE inhibitor or ARB for at least 4 weeks before screening, unless medically contraindicated. The trial did not include people with CKD who had type 1 diabetes or who had an organ transplant. The primary outcome in DAPA-CKD was a composite outcome of a sustained eGFR decline of 50% or more, end-stage renal disease or death from renal or cardiovascular causes. Results showed that the primary composite outcome occurred in 9.2% of people having dapagliflozin, compared with 14.5% of people having placebo (hazard ratio [HR] 0.61, 95% confidence interval [CI] 0.51 to 0.72). Clinical advice to the ERG suggested that the management of CKD in DAPA-CKD was broadly generalisable to UK clinical practice. However, the ERG highlighted that DAPA-CKD did not give clinical efficacy evidence for

some groups of people with CKD who would be included in the marketing authorisation for dapagliflozin. These included people:

- not having optimised ACE inhibitors or ARBs
- with a uACR of less than 22.6 mg/mmol
- with an eGFR of less than 25 ml/min/1.73 m^2 or more than 75 ml/min/1.73 m^2
- who had an organ transplant.

The clinical experts considered that there would likely be benefits in starting dapagliflozin in people with an eGFR of between 15 ml/min/1.73 m^2 and 25 ml/min/1.73 m^2, despite the lack of clinical evidence. However, one expert noted the uncertainty in this population, as well as concerns with the impact of a transient decrease in eGFR associated with SGLT2 inhibitors at lower eGFR levels. The committee concluded that the results from DAPA-CKD suggest that dapagliflozin plus standard care is more effective than standard care alone. But, it noted that DAPA-CKD tested dapagliflozin only in an enriched population with greater potential to benefit from treatment. The results may therefore not necessarily be transferrable to the groups of people with CKD excluded from DAPA-CKD.

DECLARE-TIMI-58 and DAPA-HF provide evidence for some people excluded from DAPA-CKD, but evidence gaps remain

3.8   The company presented additional clinical evidence from 2 randomised controlled trials, DECLARE-TIMI-58 (n=17,160) and DAPA-HF (n=4,744). This was to provide renal outcome data across a broader population. DECLARE-TIMI-58 included people with type 2 diabetes who had, or were at high risk of, cardiovascular events, and who had a creatinine clearance of 60 ml/min/1.73 m^2 or more. However, 7.4% of people (n=1,265) had an eGFR of less than 60 ml/min/1.73 m^2. Inclusion in DECLARE-TIMI-58 was not restricted based on uACR level, so the trial is likely to have enrolled people across a wide range of uACR levels. DAPA-HF included people

with heart failure with reduced ejection fraction, regardless of whether they had comorbid type 2 diabetes. People in DAPA-HF had to have an eGFR of 30 ml/min/1.73 m^2 or more, and uACR was not measured. Both DECLARE-TIMI-58 and DAFA-HF included some people with comorbid CKD (34.8% and 40.7%, respectively). Neither study included people with type 1 diabetes or who had an organ transplant. Results from DECLARE-TIMI-58 and DAPA-HF suggested that dapagliflozin plus standard care is more effective than standard care alone across the broad CKD population, regardless of uACR and eGFR levels. DECLARE-TIMI-58 showed that the dapagliflozin treatment effect was consistent between people with a uACR of less than 22.6 mg/mmol and those with a uACR of 22.6 mg/mmol or higher for the following end points: the co-primary end point of hospitalisation for heart failure or cardiovascular death, and the renal end point without cardiovascular death (eGFR decline greater of 40% or more, end-stage renal disease, or death from renal causes). However, the ERG highlighted that there remained some subgroups of people with CKD for which there was no clinical trial evidence for dapagliflozin. These included:

- people without type 2 diabetes and with a uACR of less than 22.6 mg/mmol
- people who had an organ transplant.

The ERG also noted that the data from DAPA-HF was not used in the company's economic model. The committee concluded that DECLARE-TIMI-58 and DAPA-HF showed that dapagliflozin was clinically effective in some subgroups of people with CKD outside of DAPA-CKD. However, the size of benefit in subgroups outside DAPA-CKD was uncertain, and important uncertainties and evidence gaps remained.

There is a lack of evidence for dapagliflozin in people with CKD who have had an organ transplant

3.9　　The company did not present evidence for dapagliflozin in people with CKD who have had an organ transplant. Clinical experts advised that there is a lack of evidence for using dapagliflozin in these people in general. The experts highlighted that further clinical trials are needed to establish the clinical effectiveness and safety of dapagliflozin in these people. A consultation comment highlighted that evidence should be developed on the benefits of dapagliflozin for people with kidney transplants. The committee concluded that there is a lack of evidence for dapagliflozin in people with CKD who have had an organ transplant, and there is need for further clinical trials in these people.

The company's simulated outcomes analysis and real-world evidence does not robustly resolve the evidence gap for people with low uACR levels without type 2 diabetes

3.10　　In response to technical engagement, to address the lack of clinical-effectiveness evidence for dapagliflozin in people without type 2 diabetes and with a uACR of less than 22.6 mg/mmol (see section 3.8), the company provided an additional analysis. This estimated outcomes for people with low uACR levels, split by whether or not they had type 2 diabetes. The company did a simulated treatment outcomes analysis using a Poisson model to fit an estimated yearly event rate conditional on uACR as the continuous variable from DAPA-CKD, with a uACR range extended from 3.39 mg/mmol to 565 mg/mmol. The results are academic in confidence and cannot be reported here. The ERG explained that such an analysis only supported a hypothesis that dapagliflozin might work in this population. The company had extrapolated event rates to a population in which there was no actual clinical evidence of dapagliflozin efficacy. In response to consultation, the company provided real-world evidence to support the efficacy of dapagliflozin in people without type 2 diabetes and with a uACR of less than 22.6 mg/mmol. This came from a US study of 2

databases. The ERG noted that this analysis had several limitations. It was based on small sample sizes, used a surrogate end point and was based on observational data. The committee agreed that, in the absence of robust trial evidence, the company's simulated treatment outcomes analysis and real-world evidence did not resolve the evidence gap in people with low uACR levels without type 2 diabetes.

Dapagliflozin and canagliflozin are likely to be equally effective in people with diabetic kidney disease, and the least costly option that meets individual patient needs should be used

3.11   Although it did not consider canagliflozin a relevant comparator (see section 3.5), the company presented an indirect comparison to estimate the efficacy of dapagliflozin compared with canagliflozin for people with CKD and type 2 diabetes. The company did an anchored matching-adjusted indirect comparison using data from the DAPA-CKD and CREDENCE trials. CREDENCE was a randomised, double-blind trial of people with type 2 diabetes and albuminuric CKD (uACR of more than 33.9 mg/mmol) having canagliflozin or placebo. The results of the indirect comparison suggested equal efficacy between dapagliflozin and canagliflozin in people with CKD and type 2 diabetes. The ERG explained that the selection of covariates in the matching-adjusted indirect comparison was overly complex. It also highlighted that the assumption of proportional hazards (that is, the relative risk of an event is fixed irrespective of time) may not be satisfied. Therefore, the Cox proportional hazard model used by the company may not be appropriate. However, the ERG considered that despite the limitations with the indirect comparison, the overall conclusion of equal efficacy was reasonable. The clinical experts explained that there was likely to be a class effect for SGLT2 inhibitors in treating CKD. The committee considered the company's indirect comparison with canagliflozin acceptable for decision making, and that a conclusion of equal efficacy for dapagliflozin and canagliflozin in people with diabetic kidney disease was reasonable. It was not presented

with any evidence suggesting a distinction between dapagliflozin and canagliflozin for people with diabetic kidney disease. It concluded that the least costly option of the 2 that meets individual patient needs should be used.

Adverse events

The adverse event profile of dapagliflozin for CKD is consistent with other licensed indications for dapagliflozin

3.12   The adverse event profile of dapagliflozin for treating CKD in the company submission was informed by evidence from DAPA-CKD. Dapagliflozin was associated with fewer deaths resulting from adverse events. There were also fewer serious adverse events with dapagliflozin compared with placebo. However, dapagliflozin was associated with a higher rate of serious adverse events among people with type 2 diabetes compared with those without type 2 diabetes. Nobody experienced diabetic ketoacidosis with dapagliflozin, and people having dapagliflozin had lower rates of major hypoglycaemic events, renal events, amputations, fractures and symptoms of volume depletion compared with placebo. The ERG explained that the adverse event profile of dapagliflozin for CKD from DAPA-CKD was generally consistent with other indications such as diabetes and heart failure. The committee noted this, and concluded that the adverse event profile of dapagliflozin in CKD is consistent with the other licensed indications for dapagliflozin.

Economic model

The company's economic model structure is appropriate

3.13   The company developed a de novo health economic model to assess the cost effectiveness of dapagliflozin plus standard care compared with standard care alone for people with CKD. The model used a cohort-level state transition approach with 6 health states defined according to CKD stages 1 to 5 (including stages G3a and G3b), with additional states for

dialysis, kidney transplant and death. It used a lifetime horizon and a cycle length of 1 month. A yearly discount rate of 3.5% was applied to costs and outcomes. Clinical Practice Research Datalink (CPRD) data informed patient baseline characteristics. CPRD is a real-world research service that collects patient data from a network of general practices across the UK. It links this to a range of other health-related data to provide a longitudinal, representative UK population health dataset. Some event risks in the model (mortality, hospitalisation for heart failure, and acute kidney injury) were also adjusted to match the CPRD data. However, the probabilities of transitioning between CKD stages were not similarly adjusted. The ERG and its clinical advisers considered the company's overall model structure to be reasonable, but noted concerns about the overall survival predictions (see section 3.17). The company assumed that dapagliflozin would not need any additional appointments or tests beyond those already associated with managing CKD. The committee was uncertain whether this would be the case, particularly for people without type 2 diabetes. Therefore, the costs for dapagliflozin may have been underestimated in the model for these people. However, the committee concluded that the company's overall model structure was appropriate.

Given the differences in available evidence, the 3 subgroups should be considered separately during decision making

3.14   To address ERG concerns at technical engagement about the lack of clinical evidence in some groups of people with CKD (see section 3.7), the company provided an updated economic model. The updated model included a revised patient population having optimised ACE inhibitors or ARBs, and the CPRD population used by the company to adjust the model was updated to reflect this. Also, the model used data from a subgroup of people with CKD from DECLARE-TIMI-58. The company presented a weighted economic analysis for the following subgroups according to their prevalence in the updated CPRD dataset:

- Subgroup 1: uACR of 22.6 mg/mmol or more, with or without type 2 diabetes.
- Subgroup 2: uACR of less than 22.6 mg/mmol, with type 2 diabetes.
- Subgroup 3: uACR of less than 22.6 mg/mmol, without type 2 diabetes.

The updated model re-estimated patient characteristics, mortality risks and transient event risks for each subgroup based on the relevant CPRD dataset. The ERG highlighted that subgroup 1 most closely reflected the DAPA-CKD population and that DECLARE-TIMI-58 also provided clinical evidence for subgroup 2, but there was no direct clinical evidence in subgroup 3. The company's updated model assumed that the CKD stage transition probabilities in subgroup 3 were the same as in subgroup 2. It also assumed that the overall survival model was the same in all 3 subgroups, except a non-type 2 diabetes adjustment factor was applied for subgroup 3. The ERG did not consider the company's weighted analysis to be appropriate, given the differences in the availability and strength of the evidence for each subgroup. Subgroup 1 was closest to DAPA-CKD but represented a small proportion of the overall weighted economic analysis, with most of the quality-adjusted life years (QALYs) and costs in the model informed by subgroups 2 and 3. The committee was concerned that subgroup 3 accounted for around one third of the company's weighted population in the cost-effectiveness analyses updated after consultation (see section 3.15), in which there is no direct clinical evidence for dapagliflozin. It agreed with the ERG that the 3 subgroups should be considered separately in decision making.

The company's updated CPRD adjustment is uncertain, but this is unlikely to have a large effect on the cost-effectiveness estimates for subgroup 2

3.15 The company updated its model in response to consultation to use a CPRD dataset that included people with an eGFR of 25 ml/min/1.73 m^2 to 75 ml/min/1.73 m^2 having optimised ACE inhibitors or ARBs, with or

without a diagnosis of CKD. This was intended to better reflect the population in the preliminary recommendations in the appraisal consultation document. However, clinical advice to the ERG suggested that the new CPRD dataset would include a large proportion of people who do not have CKD. The committee also heard that in the post-consultation model, the CPRD dataset for subgroup 2 and 3 was not stratified by type 2 diabetes status to reflect the population more accurately in each of these subgroups. Instead, the company used a single CPRD dataset in which around two thirds of people had type 2 diabetes and one third did not. The company noted that for subgroup 2, the cost-effectiveness estimate for dapagliflozin plus standard care compared with standard care alone was similar regardless of whether the CPRD adjustment was applied. The committee also noted that the cost-effectiveness estimates for dapagliflozin in subgroup 2 were similar based on both the technical engagement and post-consultation models. This suggested that the uncertainties around the CPRD adjustment had little effect on the cost-effectiveness results in this subgroup. However, there were much greater differences between the cost-effectiveness results in subgroup 3 depending on whether the CPRD adjustment was applied, suggesting greater uncertainty. The committee concluded that the updated CPRD adjustment was uncertain because the dataset likely included people without CKD who would not have dapagliflozin, and because it had not been stratified by type 2 diabetes status for subgroups 2 and 3. But, this did not have a large effect on the cost-effectiveness estimates for subgroup 2.

The mean age in the model should reflect the same CPRD datasets as those used to inform the other patient characteristics

3.16   In its technical engagement model the company used a mean (average) age of 64 years from a separate CPRD dataset. This included people with an eGFR of less than 90 ml/min/1.73 m^2 who were taking ACE inhibitors or ARBs but did not need to have a formal diagnosis of CKD. This was

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lower than the mean ages from the CPRD datasets used to adjust the 3 subgroups in the model, which ranged from around 74 to 78 years. The company noted that clinician input supported using the lower mean age, as did registry data. However, the ERG explained that the company's approach was inconsistent. This was because all other baseline characteristics and event risk adjustments in the model were based on subgroup-specific CPRD datasets all needing a formal CKD diagnosis. Therefore, it was inappropriate to include a mix of patient characteristics from separate groups of people from different CPRD datasets. The ERG preferred to use the subgroup-specific CPRD datasets informing the baseline characteristics and event risk adjustments for each subgroup in the model, for which the mean ages were higher than company's approach. The clinical experts noted that although there was uncertainty about what the mean age of people was in clinical practice, it was likely to be higher than that used by the company. They explained that although the mean age of people with CKD seen in secondary care was likely to be closer to the company's estimate, this may not fully represent those who would have dapagliflozin in clinical practice because people having treatment in primary care may be older. The committee considered that the mean age estimate from the separate CPRD dataset was inappropriate because it was likely that many people in this dataset did not have CKD. Also, applying a lower age estimate in a dataset with characteristics and risks estimated from an older population was inappropriate. This is because younger people do not have the same characteristics and risks as older people. In response to consultation, the company updated the mean ages in its model so that they were based on the same CPRD datasets as the other baseline characteristics. The weighted mean age in the company's updated model (around 73 years) was higher than the estimate used in its technical engagement model. The committee recalled that there were some uncertainties with the new CPRD dataset (see section 3.15). But, because the company's updated

model used the CPRD data consistently, the committee considered that the revised mean age was more appropriate.

Despite limitations in the company's approach to overall survival modelling, its impact on decision making is likely to be small

3.17 The company modelled the treatment effect of dapagliflozin on overall survival through 2 mechanisms:

- Directly, by applying a treatment-related hazard ratio for overall survival to each CKD state from a multivariable survival model to each state-specific overall survival model except transplant.
- Indirectly, by applying transition matrices that lead to slower disease progression for people having dapagliflozin plus standard care compared with standard care alone.

The ERG highlighted that when the adjustment to the CPRD dataset (see section 3.13) was removed, the company's model overestimated overall survival compared with the data from DAPA-CKD. The ERG was uncertain about the cause of this, but it may have been because:

- The company had included a post-randomisation covariate (CKD stage), which can lead to problems in determining causality.
- The company estimated state-specific mortality risks using a 'mean of covariates' approach, which has been shown to lead to bias when estimating survival distributions.

However, the ERG noted that even if the issues identified in the company's approach to overall survival modelling were resolved, the incremental cost-effectiveness ratio for dapagliflozin compared with standard care would likely remain below £20,000 per QALY gained in the DAPA-CKD population. The committee concluded that despite the limitations with the company's approach to overall survival modelling, its impact on decision making was likely to be small.

Cost-effectiveness estimates

Dapagliflozin is cost effective in the population represented in DAPA-CKD

3.18   The committee recalled that it would consider the company's 3 subgroups separately in decision making (see section 3.14). It considered the cost effectiveness of dapagliflozin plus standard care compared with standard care alone in subgroup 1 (people with a uACR of 22.6 mg/mmol or more, with or without type 2 diabetes). In the company's updated model in response to consultation, dapagliflozin plus standard care dominated standard care in this subgroup (that is, it was more effective and less costly than standard care). However, the committee recalled that the evidence was weaker for dapagliflozin outside of the eGFR levels in DAPA-CKD. It also noted that dapagliflozin was likely to have a large impact on NHS resources given the size of the patient population (see section 3.1), and so it needed to see robust clinical and cost-effectiveness evidence. It concluded that the cost-effectiveness estimate for dapagliflozin in subgroup 1 was an acceptable use of NHS resources. The recommended population should be limited to the eGFR and uACR levels included in DAPA-CKD (see section 3.7) to match the available evidence.

Dapagliflozin is cost effective for people with a uACR of less than 22.6 mg/mmol and type 2 diabetes

3.19   The committee considered the cost effectiveness of dapagliflozin plus standard care compared with standard care alone in subgroup 2 (people with a uACR of less than 22.6 mg/mmol and type 2 diabetes). In the company's updated model in response to consultation, the incremental cost-effectiveness ratio (ICER) for dapagliflozin plus standard care compared with standard care in this subgroup was around £6,000 per QALY gained. The recommendations in NG28 state that for people with type 2 diabetes and CKD, in addition to an ARB or an ACE inhibitor, an SGLT2 inhibitor should be considered if their ACR is 3 mg/mmol to

30 mg/mmol and offered if their ACR is higher than 30 mg/mmol (see section 3.5). Although the committee was aware of this broader context, it was mindful that its remit was to appraise the clinical and cost effectiveness of dapagliflozin. It consequently focused its decision making on the evidence provided for this technology appraisal. It recalled that DECLARE-TIMI-58 provided evidence for the treatment effect of dapagliflozin in people with CKD and type 2 diabetes with a uACR of less than 22.6 mg/mmol (see section 3.8). The committee also understood that the company had used this evidence to inform the cost-effectiveness estimate of dapagliflozin in subgroup 2 in its updated model (see section 3.14). The committee noted that the ICER in this subgroup was comfortably within what NICE considers an acceptable use of NHS resources. In response to consultation, the company provided further subgroup analysis of subgroup 2. It divided subgroup 2 into people with a uACR of less than 3 mg/mmol, and people with a uACR of 3 mg/mmol to 22 mg/mmol. The ICERs for both these subgroups were similar to the ICER for subgroup 2 as a whole (around £6,000 per QALY gained). The committee therefore concluded that dapagliflozin can be recommended for people with CKD with a uACR of less than 22.6 mg/mmol and type 2 diabetes.

Dapagliflozin cannot be recommended in people with a uACR of less than 22.6 mg/mmol who do not have type 2 diabetes

3.20   The committee considered the cost effectiveness of dapagliflozin plus standard care compared with standard care alone in subgroup 3 (people with a uACR of less than 22.6 mg/mmol without type 2 diabetes). In the company's updated model in response to consultation, the ICER for dapagliflozin plus standard care compared with standard care in this subgroup was around £17,000 per QALY gained. There was no direct clinical evidence informing subgroup 3 in the company's model (see section 3.8), and there was uncertainty around the CPRD adjustment in this subgroup (see section 3.15). This generated considerable uncertainty

in the plausibility of the cost-effectiveness estimates for this population. The committee noted a stakeholder's comment that the benefits of dapagliflozin in preventing decline in renal function should be weighed against the potential consequences of overprescribing and drug interactions, particularly in people with milder disease. It also understood from the company at the second appraisal committee meeting that subgroup 3 is likely to comprise more of the CKD population than the CPRD data suggests. Therefore, the committee considered that the consequence of decision error was likely to be higher for this subgroup. It concluded that dapagliflozin cannot be recommended for the population in subgroup 3.

Innovation

Dapagliflozin is an innovative treatment for CKD, but all relevant benefits are reflected in the cost-effectiveness estimates

3.21   The company considered dapagliflozin to be innovative because it addresses a significant unmet need in CKD, which is associated with a significant clinical and economic burden and for which standard care is inadequate for many people. The patient and clinical experts highlighted the lack of effective pharmacological management for CKD and the importance of slowing down disease progression. Patient experts felt that dapagliflozin offers a step change for treating CKD, because its ability to delay disease progression offers real hope. Clinical experts highlighted that the benefits of dapagliflozin are distinct from a blood glucose reduction alone, and that reducing progression to end-stage renal disease will increase quality of life. The committee acknowledged the new benefits offered by dapagliflozin and other SGLT2 inhibitors as additional treatment options for CKD. However, it concluded that it had not been presented with evidence of any additional benefits that were not captured in the QALY measurements.

Equalities considerations

There are no equalities issues relevant to the recommendations

3.22   No equalities issues were raised during scoping stage. During technical engagement, patient and clinical expert submissions highlighted that CKD disproportionally affects people from Black, Asian, and minority ethnic groups and lower socioeconomic backgrounds. People from these groups are also more likely to have CKD that progresses quicker to kidney failure and to die earlier. During consultation, a consultee also highlighted that use of ACE inhibitors or ARBs differs by ethnicity and socioeconomic status. However, the committee did not consider these to be equality issues that could be resolved by this appraisal. No other potential equality issues were raised. The committee concluded that there were no equalities issues relevant to the recommendation.

4   Implementation

4.1   [Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013](#) requires 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 chronic kidney disease 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 of the guidance. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Megan John
Chair, appraisal committee
January 2022

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 D.

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.

Zain Hussain

Technical lead

Charlie Hewitt

Technical adviser

Kate Moore

Project manager

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