NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Finerenone for treating chronic kidney disease in type 2 diabetes

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

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

The appraisal 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 race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: May 2022

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

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 6 June 2022

Second appraisal committee meeting: 9 June 2022

Details of membership of the appraisal committee are given in section 5

1 Recommendations

1.1 The committee was minded not to recommend finerenone as an option for treating stage 3 and 4 chronic kidney disease with albuminuria associated with type 2 diabetes in adults.

1.2 The committee recommends that NICE requests further clarification and analyses from the company, which should be made available for the second appraisal committee meeting, and should include:

- a comparison of finerenone with sodium–glucose cotransporter-2 (SGLT2) inhibitors
- all data from the FIGARO-DKD and FIDELITY studies that are directly relevant to the decision problem in this appraisal
- updating the effectiveness data in the cost-effectiveness model with new point estimates from the additional clinical data
- cost-effectiveness scenario analyses of finerenone used at second line (compared with SGLT2 inhibitors in an SGLT2 inhibitor-naive population) and at third line (as an add-on to second-line SGLT2 inhibitors in an SGLT2 inhibitor-experienced population)
- comparisons of transition probabilities over time, and model predictions of time to events compared with empirical data from the trial
- base cases with both trial-based utilities and utilities from literature sources that are more recent and relevant than currently used in the model
- scenario analyses of alternative treatment waning effects for finerenone.
- a valid probabilistic sensitivity analysis that includes accounting for parameter uncertainty in transition probabilities to reflect CKD progression

Why the committee made these recommendations

Standard care for chronic kidney disease in people with type 2 diabetes includes angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and SGLT2 inhibitors. Finerenone would be used after ACE inhibitors and ARBs, and could be given before, after, or with SGLT2 inhibitors.

The clinical evidence suggests that, when compared with placebo plus standard care, finerenone plus standard care improves kidney function and helps to slow the worsening of disease. But there were not enough people in the trial to provide enough data to be certain. Also, the company did not compare finerenone with SGLT2 inhibitors, and it did not present evidence from other studies that may have helped to reduce the uncertainty.

Because of this, the cost-effectiveness estimates are highly uncertain. So, the committee was minded not to recommend finerenone until these uncertainties have been explored further.

2 Information about finerenone

Marketing authorisation indication

2.1 Finerenone (Kerendia, Bayer) is indicated 'for the treatment of chronic kidney disease (stage 3 and 4 with albuminuria) associated with type 2 diabetes in adults.'

Dosage in the marketing authorisation

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

Price

2.3 The indicative list price of finerenone is £55.20 for a 30-day supply of 30 tablets, for both 10 mg and 20 mg doses, and a daily cost of £1.84 (excluding VAT, company submission). Costs may vary in different settings because of negotiated procurement discounts.

3 Committee discussion

The appraisal committee considered evidence submitted by Bayer, 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 condition

There is an unmet need for treatment options for chronic kidney disease associated with type 2 diabetes

3.1 Chronic kidney disease (CKD) is a long-term condition involving abnormal kidney function or structure. It is affected by other comorbidities, particularly type 2 diabetes. The excess glucose in type 2 diabetes can further affect kidney function, and accelerate CKD progression. In severe cases, dialysis or transplant can sometimes be needed. It is estimated that around 3 million people have type 2 diabetes in the UK and around 20% of these will need kidney disease treatment. The clinical experts commented that people with CKD and type 2 diabetes have significant additional risk of morbidity (including end stage renal disease) and premature mortality compared with people with CKD alone. This is particularly because they are at higher risk of cardiovascular disease. The clinical experts added that the aim of treatment is to slow progression of disease. They described current treatments, which focus on lifestyle changes, using angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), as well as increasing use of sodium–glucose cotransporter-2 (SGLT2) inhibitors because of the recent recommendations in the NICE guideline on the management of type 2 diabetes in adults (NG28) and dapagliflozin for treating chronic kidney disease (TA775). The clinical experts emphasised the need for additional therapies for people with CKD and type 2 diabetes because of the residual risk of progressive deterioration in kidney function, despite current therapies. They also highlighted complications such as foot ulcers and the need for amputations, in addition to needing dialysis or

transplants. The clinical experts explained that comorbidities can prevent people from having dialysis. The patient expert submission highlighted the limited treatment options in this disease area, especially where SGLT2 inhibitors are not suitable, and that new options would be welcomed. The committee also acknowledged that younger people and people from certain family backgrounds were at more risk of disease progression. The committee concluded that there is an unmet need for additional therapies for CKD associated with type 2 diabetes.

Treatment pathway

Finerenone is likely to be prescribed in secondary care to begin with, but will eventually be prescribed in primary care

3.2 The clinical experts expected that people with type 2 diabetes and proteinuria (which is elevated protein in the urine, indicating that the kidneys may be damaged) would be seen by nephrologists in secondary care. They stated that new treatments are usually prescribed in secondary care initially, and, as familiarity with the treatment increases, they eventually transition to primary care. However, they noted that people who may be eligible for finerenone treatment may not always be receiving care in secondary care settings. The committee noted that the setting in which finerenone is prescribed is important when considering the confidential discounts of treatments used in standard care, and therefore the cost-effectiveness estimates. This is because some confidential discounts may not be available in primary care. The committee concluded that finerenone may initially be prescribed in secondary care, but will likely be prescribed in primary care once experience grows.

Finerenone would be offered after ACE inhibitors and ARBs, but its positioning relative to SGLT2 inhibitors is unclear

3.3 Finerenone is indicated for stage 3 and 4 CKD with albuminuria (with albuminuria defined in the licence as a minimum urine albumin to creatinine ratio of 3 mg/mmol). People with stage 3 or 4 CKD with

albuminuria usually receive ACE inhibitors, ARBs or both, at the maximum tolerated licensed dose, as first-line therapy. Second-line SGLT2 inhibitors can be added, in line with NG28 and TA775. The company explained that it did not expect finerenone to replace existing therapies, because it has a different mode of action. Rather, it expands on current treatment options. The company also did not view SGLT2 inhibitors as established treatments currently in the NHS. Therefore, the company submission focused on finerenone as a second-line treatment, where it would be added to first-line ACE inhibitors and ARBs. The clinical experts stated that although SGLT2 inhibitors were only recently recommended by NICE, their use is expected to increase, although this could take time. They also noted that a range of therapies are needed to target different causes of kidney damage, and that all of these treatments will likely work together for better renal protection than any of them alone. The committee agreed that finerenone and SGLT2 inhibitors would be used after the maximum tolerated dose of ACE inhibitors and ARBs, but noted that which treatment would be chosen first was unclear. The clinical experts agreed that finerenone and SGLT2 inhibitors would be positioned sequentially in the treatment pathway, with the second treatment (after first-line ACE inhibitors and ARBs) depending on tolerance and proteinuria incidence. They agreed that which treatment would be chosen first is unclear, because both are new. However, they would not both be started at the same time. The clinical experts described instances in which SGLT2 inhibitors may be preferred, for example with hyperkalaemia, and instances where finerenone may be preferred, for example if there was a risk of diabetic ketoacidosis and foot disease. The committee concluded that in theory, finerenone could be given before or after SGLT2 inhibitors, depending on people's individual circumstances. However, clinical and cost-effectiveness analyses comparing finerenone with SGLT2 inhibitors would further inform this decision (see section 3.4).

SGLT2 inhibitors are a relevant comparator because their use is likely to increase and become standard care

3.4 The company did not include SGLT2 inhibitors as a comparator in its decision problem, because it did not view SGLT2 inhibitors as established NHS practice. The company referenced a low percentage market share by volume of SGLT2 inhibitors compared with oral or parenteral hypoglycaemics, and uncertainty about the proportions that are used for CKD associated with type 2 diabetes. The committee noted that in the FIGARO-DKD study, the proportion of people taking SGLT2 inhibitors was higher than in the FIDELIO-DKD study, which was completed a year earlier (see section 3.5), suggesting increased use of SGLT2 inhibitors. However, the company and clinical experts noted that in this case, the SGLT2 inhibitors were used for lowering glucose. The committee recognised that SGLT2 inhibitors were not established NHS treatment for CKD during the FIDELIO-DKD and FIGARO-DKD trials, but could still be considered a relevant comparator in the future. It noted that the recent NICE recommendations will likely increase uptake at a faster rate. The clinical experts agreed that SGLT2 inhibitor use is likely to increase, and that finerenone and SGLT2 inhibitor therapy would be used in combination, sequentially, unless either drug is not tolerated (see section 3.3). The ERG suggested that, because of the multiple potential places of finerenone in the pathway, multiple approaches could be used to compare finerenone with SGLT2 inhibitors. This could include an indirect treatment comparison, with finerenone as an alternative to SGLT2 inhibitors, or a comparison of finerenone in addition to SGLT2 inhibitors using trial data (although there would be small sample sizes). The ERG noted that the trial and model are not informative enough to show the comparisons of finerenone with SGLT2 inhibitors in its current state. Spironolactone, a steroidal mineralocorticoid receptor antagonist, was also discussed, but the committee did not consider it relevant for CKD associated with type 2 diabetes. This was because there was a lack of comparative trial evidence and the clinical experts agreed that finerenone and spironolactone are

different and used in different contexts. The committee agreed that SGLT2 inhibitor use will increase and become incorporated into standard practice. Therefore, the committee concluded that SGLT2 inhibitors are a relevant comparator.

Clinical evidence

FIDELIO-DKD is a relevant clinical trial but further evidence from FIGARO-DKD would be preferred

3.5 The clinical effectiveness evidence for finerenone is from the FIDELIO-DKD trial. This was a phase 3, randomised, double-blind, multicentre, placebo-controlled trial that enrolled over 5,000 adults with CKD and type 2 diabetes in the full analysis set. The inclusion criteria included:

- an albumin to creatinine ratio of 3.4 mg/mmol to less than 33.9 mg/mmol, an eGFR of 25 ml/min/1.73 m^2 to less than 60 ml/min/1.73 m^2, and diabetic retinopathy

or

- an albumin to creatinine ratio of 33.9 mg/mmol to 565 mg/mmol, and an eGFR of 25 ml/min/1.73 m^2 to less than 75 ml/min/1.73 m^2.

People took 10 mg or the target 20 mg of finerenone, once daily in addition to standard care. In the full analysis set, 14 people (0.25%) were not receiving any ACE inhibitors or ARBs at baseline. The proportions of ACE inhibitors or ARBs at baseline in the marketing authorisation population were in line with the full analysis set. Therefore, the committee agreed that the marketing authorisation population was in line with the company's proposed positioning of finerenone (see section 3.3).
Follow up was every 4 months including after discontinuation, with the final follow up being 4 weeks and 5 days after the last dose of the study drug. The primary outcome was the time to the first event of a composite end point consisting of: onset of kidney failure, a sustained decrease of estimated glomerular filtration rate (eGFR) of 40% or more from baseline

over at least 4 weeks, or renal death. The data and results from the population covered by the marketing authorisation (approximately 89% of the study population) were presented to committee. However, the committee noted that the trial was powered for the full analysis set rather than the marketing authorisation population. The clinical experts were satisfied that the baseline characteristics reflected the population that would be seen in the NHS, in particular noting a good balance of family backgrounds including a significant number of people from Asian family backgrounds. There was a relatively low proportion of people using SGLT2 inhibitors at baseline, which the clinical experts suggested was because at the time of study, SGLT2 inhibitors were used for glycaemic control only, and, at the beginning of the trial, were contraindicated for people with an eGFR of less than 60 ml/min/1.73 m^2 (this restriction no longer exists in NHS practice). Therefore, SGLT2 inhibitors would have been actively discouraged for the marketing authorisation population because it included people with an eGFR of less than 60 ml/min/1.73 m^2. The committee was also aware of the FIGARO-DKD phase 3 trial, which the company excluded from its evidence base because the full data was not available at the time of the submission. The primary outcome in FIGARO-DKD was a composite cardiovascular end point, and the key secondary end point matched the primary end point in FIDELIO-DKD. There were some differences in the inclusion criteria between the trials, with more early-stage CKD allowed in FIGARO-DKD. The clinical experts agreed that although the trial populations were different, there was significant overlap, so that some patients could have entered either study. A further meta-analysis called FIDELITY pooled results from FIDELIO-DKD and FIGARO-DKD. The committee thought that a similar analysis would provide additional insight into the marketing authorisation population. Although a clinical expert commented that they would feel confident using data from FIDELIO-DKD if this was the only trial available, the committee was uncertain that all the potentially relevant evidence had been presented. This was because the results from FIDELIO-DKD were

underpowered for the marketing authorisation population, and evidence from additional trials could give further supportive evidence and reduce uncertainty (see section 3.7). Therefore, the committee concluded that although FIDELIO-DKD, the key clinical trial, was relevant, FIGARO-DKD also contains relevant data, and combining the 2 would strengthen the evidence base.

The eGFR ranges in the marketing authorisation are appropriate

3.6 The marketing authorisation defines stage 3 and 4 CKD as an eGFR of 25 ml/min/1.73 m^2 or greater. This differs to the definition used by the NHS, which is an eGFR of 15 to less than 60 ml/min/1.73 m^2. The clinical experts explained that in practice, each decline in eGFR is looked at individually, rather than as CKD stages. In addition, the clinical experts reported that from a patient perspective, the percentage of kidney function is the main concern. They were therefore satisfied with the CKD stages defined in the marketing authorisation. The ERG noted a lack of clarity about finerenone use when the eGFR is between 15 and 25 ml/min/1.73 m^2 because people in this category have CKD stage 4, and the company's submission did not include an analysis of this population. The company explained that the trial only enrolled people with an eGFR of 25 ml/min/1.73 m^2 and above, and although 2.4% of people in the trial had an eGFR below this, their eGFR had deteriorated in the time between screening and randomisation. The ERG was satisfied with the analyses presented at technical engagement. The committee noted that the marketing authorisation does not recommend starting finerenone with an eGFR of less than 25 ml/min/1.73 m^2, but:

- it allows continuation if the eGFR drops below this
- if the eGFR is 15 ml/min/1.73 m^2 or more, finerenone use can continue with dose adjustment according to serum potassium
- if the eGFR falls below 15 ml/min/1.73 m^2, that is end stage CKD, and finerenone should be discontinued because of limited data.

The clinical experts did not expect the eGFR ranges in which SGLT2 inhibitors would be used would influence the treatment pathway, because they expected SGLT2 inhibitors to be used widely because of their many indications. The finerenone marketing authorisation specifies that people must have albuminuria, which the company defined as at least 3 mg/mmol urine albumin, because this was the cut-off used in FIDELIO-DKD. However, the degree of albuminuria does not affect finerenone use. The clinical experts commented that the greater the degree of albuminuria, the more potential benefit a person will have from additional therapies. The committee concluded that although the marketing authorisation did not cover all of stage 3 and 4 CKD as defined by the NHS, the eGFR ranges specified by the company were appropriate for likely finerenone use.

The primary composite outcome is appropriate, but the results for the population in the marketing authorisation are underpowered

3.7 The components of the primary composite outcome of FIDELIO-DKD (see section 3.5) were kidney failure (and its subcomponents: end stage renal disease and a sustained decrease in eGFR of less than 15 ml/min/1.73 m^2), a sustained decrease in eGFR of 40% or more from baseline, and death from renal causes. The committee noted that of these components, only 1 result was statistically significant. However, the company emphasised that the study was not powered for the components of the primary composite outcome. Rather, it was only powered for the primary composite outcome for the full analysis set. The ERG accepted that the primary composite outcome is clinically relevant. At technical engagement, the company did statistical analyses to assess heterogeneity (that is, the interaction between components of the composite endpoint), and did not identify any heterogeneity. However, the ERG stated that the company's test for heterogeneity would also be underpowered if the trial itself was underpowered for individual components. So, the committee acknowledged that all outcomes presented were underpowered because the licence is based on a subset of the population, and the trial was only powered for the full population.

Despite this, the clinical experts and committee acknowledged that numerically, if not always statistically, the components of the composite outcome were consistent in favouring finerenone. The clinical experts explained that the trial would have to be a lot longer for all the components to be individually powered. They further clarified that death from renal causes is a rare outcome in clinical trials because it only occurs in people who do not have dialysis. The committee understood that the composite outcome components are not mutually exclusive, so each component is a smaller subset of the same people. It also understood that wider confidence intervals are expected for rarer events. The clinical experts agreed that the primary composite outcome was clinically relevant. The committee agreed that renal outcomes from FIGARO-DKD (see section 3.5) would have been useful, but acknowledged that some of the FIGARO-DKD population was not relevant in this disease area. The committee noted that the Kaplan–Meier curves had a lot of censoring and not many events, and that the company had not provided confidence intervals. This, in addition to the lack of power, emphasised the importance of additional data from FIGARO-DKD for a better powered analysis. The committee concluded that the primary composite outcome of FIDELIO-DKD is clinically relevant, but the results lack power, so further evidence from FIGARO-DKD would help augment the data.

Hyperkalaemia is the main adverse event associated with finerenone, but overall the adverse events are not concerning

3.8 The main adverse event in FIDELIO-DKD associated with finerenone was hyperkalaemia. However, the committee acknowledged that it seemed to be mild in most cases. The clinical experts agreed that the adverse events were not unexpected and noted that in the FIDELIO-DKD protocol, finerenone or placebo were withheld when serum potassium levels were greater than 5.5 mmol per litre. However, they agreed that in clinical practice, this would be allowed to go slightly above this in some circumstances. Hospitalisation rates were around 1% higher in the finerenone arm than in the placebo arm, but the clinical experts did not

see this as being a significant concern if these hospitalisations were likely for short durations. The committee concluded that hyperkalaemia is an important adverse event to consider, but overall, the adverse events results from FIDELIO-DKD are not particularly concerning.

Cost effectiveness

The company's model is structurally appropriate for decision making

3.9 The company presented a cohort-level, state-transition Markov model to estimate the cost effectiveness of finerenone plus standard care compared with placebo plus standard care. A representative treatment from each relevant class of therapy in standard care was used in the model, at its maximum dose. The ERG agreed with this approach. The clinical experts agreed that the treatments used were typical of NHS practice, but also agreed with stakeholder comments that some of the doses were lower than expected. However, if the average or most common dose was assumed, then they were not unreasonable. The committee acknowledged that any inaccuracies were likely to have a minor impact on results because they apply to both arms of the model. The health states used were CKD stage 1 or 2, CKD stage 3, CKD stage 4, CKD stage 5 without dialysis, dialysis, transplant, and death. These health states were all duplicated into a before and after cardiovascular event sub-model. The model cycle length was 4 months, in line with data collection in the trial, and a lifetime time horizon of 34.2 years was used. Originally, the utilities used in the model were 5-level EQ-5D (EQ-5D-5L) values from the trial mapped onto the EQ-5D-3L. But after technical engagement, the company updated these to utilities from the literature (see section 3.14). No treatment waning effects were included in the model (see section 3.11). The committee noted that the model showed possible large jumps in progression, for example from CKD stage 3 to CKD stage 5, and from CKD stage 3 to dialysis or transplant. The clinical experts considered this to be plausible because in clinical practice, people with CKD associated with type 2 diabetes can move between health

states, rather progress linearly. The committee noted that a shorter cycle length may have showed more intermediate states. Overall, the committee concluded that structurally, the company's model was suitable for decision making.

There are uncertainties with the simplified transition probabilities in the company's model

3.10 The individual health states in the model were empirically based on FIDELIO-DKD and applied as a 4-month probability for the whole of the model. So, the probability of transitioning from 1 state to another is repeated for the duration of the model. The ERG was concerned that assuming constant transition probabilities over time may have been an over-simplification. It added that the large FIDELIO-DKD dataset could allow for more complex transitions in the model. The company agreed, but explained that its experts had advised against this approach. The company clarified that time-varying risks are accounted for (albeit in a simplified way) because cardiovascular risk over time varies by age. The company used this approach to minimise interference with trial data, and because its health economists and clinicians had advised that its method of validating progression was reasonable. It added that its model structure was common in modelling CKD progression, and clinical expert advice was that current eGFR level is the main predictor for progression, so the same rates of cardiovascular events were applied for all people with the same CKD state. Mortality was also accounted for separately because of competing risks. The ERG agreed that the model captured the additional risk linked with age. However, overall CKD progression between health states was time invariant and the ERG determined that the model was oversimplified. To validate its approach, the company compared its model with the Study of Heart and Renal Protection (SHARP)-CKD-CVD Markov model. This validation compared the cumulative probabilities per 1,000 participants at 5 and 10 years, with 95% confidence intervals around the company model results, and ranges around the SHARP-CKD-CVD model. The company concluded that its model results were within the ranges

shown by SHARP-CKD-CVD. However, the ERG explained that although the company's model results may be within the ranges of the SHARP-CKD-CVD model, these ranges are extremes rather than confidence intervals. So, they can be obtained from varying inputs. The ERG highlighted that it is important to consider how the results are obtained, for example how events accrue over time. It noted that the tight confidence intervals observed around the company's model results in the cross validation were because of the time-invariant transition probabilities used by the company. The ERG noted that although the SHARP-CKD-CVD model could inform some parts of the company's model, this was limited because it was built for a different purpose and the populations cannot be exactly matched. For example, there were more renal replacement events in the SHARP-CKD-CVD model, but fewer people with relatively mild CKD, because the minimum CKD stage was 3b. The ERG explained that the effect of time-invariant transitions on the model output is uncertain. This is because it was not possible to assess CKD over time. The company also clarified that it had not compared transitions to the trial data. The ERG felt that validating the distribution of outputs over a time period would have been a better approach. The committee concluded that the effects of using time-invariant transition probabilities are uncertain; a comparison of transitions over time to the trial data would be informative. In particular, the committee would like to see modelling predictions of time to various events, for example cardiovascular or renal replacement therapy events, compared with empirical Kaplan–Meier curves from the relevant populations in FIDELIO-DKD and FIGARO-DKD.

Treatment effects beyond 4 years are uncertain

3.11 In the model, the company assumed that people would discontinue finerenone at the rate observed in FIDELIO-DKD. After this, people accrued the costs and effectiveness of standard care. The company explained that no treatment effect waning was explored because it claimed that in the trial, the relative effect of finerenone was almost constant over 4 years. The company also assumed that in clinical

practice, finerenone would be stopped (see section 3.12) if there was no treatment effect. The clinical experts thought that finerenone benefit is likely to be maintained over time.. They added that at more advanced CKD stages, it takes fewer events to progress to dialysis, with a large impact on quality of life. Therefore, there may be a greater absolute benefit of finerenone in more advanced CKD. The committee concluded that extrapolating relative treatment effects beyond the 4 years seen in the trial is uncertain with the current evidence. This needs to be explored further using scenario analyses exploring the effects of different approaches to extrapolating treatment benefit beyond the period covered by observed data.. This should be in line with section 5.7.7 of NICE's guide to methods of technology appraisal, where different variations of treatment effect are described.

Finerenone is stopped after renal replacement therapy starts

3.12 In the company's model, finerenone is stopped after starting renal replacement therapy. The ERG did not have a preference about whether finerenone should be stopped or continued after renal replacement therapy is started. The clinical experts stated that finerenone would be stopped if a person's eGFR dropped below 15 ml/min/1.73 m^2 (see section 3.6), which would occur before renal replacement therapy was started. The stopping rule decreased the incremental cost-effectiveness ratio (ICER) in a scenario analysis. The committee concluded that finerenone would be stopped after renal replacement therapy is started.

The company's modelling of previous cardiovascular disease is acceptable, but restructuring the model would help reduce uncertainty

3.13 The ERG explained that some people in FIDELIO-DKD would have had at least 1 previous cardiovascular event. This is because, although people were excluded if they experienced cardiovascular events in the 30 days before the screening visit, the exclusion criterion did not cover cardiovascular events that happened before this. The ERG and company agreed that 45.9% of people enter the model with a history of

cardiovascular disease. The company preferred to model this proportion of people from the point of entering FIDELIO-DKD (that is, to use the simplifying assumption that no patients had experienced a cardiovascular event before entering the model), whereas the ERG preferred to model this using the total patient history. The ERG explained that the company used external evidence to inform mortality and that this has a substantial effect on the cost-effectiveness estimates. Therefore, there is a risk that estimates will be biased if the proportion of people with a history of cardiovascular disease is not accurate. The company explained that the model was structured in a way that meant that if it included total cardiovascular history, a considerable part of the cardiovascular protective benefit of finerenone would be lost. The ERG suggested that it would be ideal to have 3 sub-models, reflecting:

- people with no cardiovascular history
- people entering the model with cardiovascular history but yet to experience a further cardiovascular event
- people who have experienced a cardiovascular event in the model.

The committee agreed that in the company's 2 sub-model, both the company and the ERG had valid reasons to support the different approaches, and that neither approach was optimal. It agreed that it would not be fair to lose any cardiovascular benefit that finerenone is associated with, but noted that this benefit was not statistically significant in the trial. The committee also noted that any limitations in the company's sensitivity analyses (see section 3.15) mean that uncertainties around this benefit cannot be analysed with a valid probabilistic sensitivity analysis. The committee concluded that the company's approach likely resulted in optimistic cost-effectiveness results, and restructuring the model into 3 sub-models would reduce uncertainty.

There is uncertainty about the most appropriate utility values to use in the model

3.14 The company initially used empirical data from FIDELIO-DKD to inform the utilities used in its model because they were trial based and it considered them to be conservative. However, after technical engagement, the company decided to use utility sources from the literature. This was because the ERG was concerned about an apparent increase in utility from CKD stages 1 to 2, to CKD stage 3. The company still used FIDELIO-DKD to inform CKD stage 1 to 2 utilities, but the utilities for all other health states were changed to be consistent with the NICE technology appraisal guidance on tolvaptan for treating autosomal dominant polycystic kidney disease (TA358). This was decided because it included the necessary utilities for the health states, and it was previously accepted by NICE. The ERG noted that it had merely raised questions about some utility values used in the company's submission, and it had not directed the company to completely revise its approach. It noted that the CKD-based health utilities from TA358 were from a study from 2005, with a small relevant population, and it did not use the EQ-5D. The company reviewed relevant literature in its submission that included more recent studies to parametrise comparable health states in recent NICE guidelines: Type 2 diabetes in adults: management NG28), acute kidney injury: prevention, detection and management (NG148) and chronic kidney disease (NG203). However, it did not appear to have used them to parametrise its model. The ERG preferred using modified trial-based utilities, despite some imperfections. The utilities from the trial and updated utilities from the literature were similar for CKD stages 3 and 4, but lower for the subsequent stages from TA358. The company acknowledged that CKD health states were determined from TA358, which evaluated a different indication, but it had advice from clinicians that it is not CKD stage 5 and dialysis, but being on dialysis itself, that has a large impact on quality of life. The clinical experts explained that there is not a large difference in the quality of life between CKD stage 1 to 2 and

CKD stage 3 because CKD stage 3a and 3b is generally asymptomatic, although renal function is affected physiologically. However, the clinical experts noted that with CKD and type 2 diabetes, there are more comorbidities, with a greater burden, and therefore a lower quality of life. In addition, people with CKD and type 2 diabetes tend to progress between CKD stages at a faster rate for any given eGFR level. The ERG and committee acknowledged that in the trial, the utilities for dialysis, post-dialysis and transplant were higher than expected. The committee concluded that both approaches to utilities in the model have advantages and disadvantages, so a base case with trial-based utilities, and another with utilities from more recent and relevant literature sources than those currently used in the model, such as utilities from NG28, would be informative.

The probabilistic and deterministic sensitivity analyses have limitations, adding to uncertainty in the cost-effectiveness estimates

3.15 The ERG described the company's sensitivity analyses as having multifaceted issues. These included issues of grouping parameters, having wide parameter bounds, parameters being sampled from user-specified limits, and the overestimation of uncertainty in utility values. Moreover, the critical transition probabilities are not only time-invariant, they are not subject to any form of sensitivity analysis. The company attempted to address these uncertainties and its rationale during technical engagement. It explained that certain parameters were grouped to account for a higher utility being observed for CKD stage 3 than CKD stage 1 to 2. However, the company changed its utility source in the model (see section 3.14). The ERG did not agree with the approach because the differences in values in the probabilistic sensitivity analysis were not shown, only whether the values were all high or all low. The ERG highlighted that using very wide parameter bounds stress tests the deterministic sensitivity analyses to implausible limits. The company acknowledged its lack of inclusion of uncertainty from its time-invariant transition probabilities is a limitation, but also that this concerns the impact

of finerenone in delaying CKD progression, which is significant in the trial. The company described how the probabilistic sensitivity analysis could include the statistical impact of finerenone to translate to an improvement in benefit when randomisation occurs. The company acknowledged the limitations in the sensitivity analyses and mentioned that it would not be able to resolve all the problems, in particular those to do with utilities. The committee acknowledged that the outputs of the sensitivity analyses should be interpreted with caution, and that the company's approach to the probabilistic sensitivity analyses is flawed.

Cost effectiveness estimates

The current clinical evidence is not in line with the committee's preferences

3.16 The committee felt it had not been presented with the fundamental data that would be needed to make a decision about the cost effectiveness of finerenone. It would prefer the company to do the following:

- Present analyses with SGLT2 inhibitors as a comparator (see section 3.4).
- Present analyses on the different sequences of using finerenone and SGLT2 inhibitors at second and third line. That is, standard care followed by an SGLT2 inhibitor at second line and finerenone at third line, or standard care followed by finerenone at second line and an SGLT2 inhibitor at third line (see section 3.3).
- Present analyses that include relevant data from FIGARO-DKD to reduce the uncertainty in the results for the population in the marketing authorisation (see section 3.5).
- Update the effectiveness data in the model using updated point estimates from the new clinical data (see section 3.7).

The committee acknowledged the uncertainties in the model and the associated uncertainties in the sensitivity analyses. The committee concluded that:

- Comparisons of transition probabilities over time in the model and model predictions of time to events against empirical data from the trial should be presented (see section 3.10).
- Scenario analyses of alternative approaches to extrapolating treatment effects for finerenone should be presented (see section 3.11).
- Finerenone treatment would stop following the start of renal replacement therapy (see section 3.12).
- Both the company and ERG approaches to modelling history of cardiovascular disease have problems. There is uncertainty about the impact on the ICER, but restructuring the model with 3 sub-models can reduce the uncertainty (see section 3.13).
- Utilities from the trial and literature have advantages and disadvantages, and a base case with trial-based utilities and another with utilities from recent and relevant literature sources that include those used in recent NICE guidelines and utilities identified in the company's submission should be explored for more reliability (see section 3.14).
- A valid probabilistic sensitivity analysis is needed, in particular accounting for parameter uncertainty in transition probabilities reflecting CKD progression (see section 3.15)

Other factors

There are no equality issues

3.17 No equality or social value judgement issues were identified that were not captured in the modelling.

Conclusion

Finerenone cannot be recommended with the current evidence base

3.18 The committee agreed that gaps in the clinical evidence base, in particular with the missing SGLT2 inhibitor comparator and uncertainties in the modelling, meant that any cost-effectiveness estimates would be highly uncertain. Therefore, it was minded not to recommend finerenone for treating CKD associated with type 2 diabetes with the current evidence base.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review 3 years after publication of the guidance. NICE welcomes comment on this proposed date. NICE will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Charles Crawley
Chair, appraisal committee
April 2022

5 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.

Summaya Mohammad
Technical lead

Carl Prescott
Technical adviser

Daniel Davies
Project manager

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