

## 7.07 FINERENONE, Tablet 10 mg, Tablet 20 mg, Kerendia<sup>®</sup>, Bayer Australia Ltd.

### 1 Purpose of submission

- 1.1 The standard re-entry resubmission requested a General Schedule Authority Required (STREAMLINED) listing for finerenone for the treatment of chronic kidney disease (CKD) in patients with type 2 diabetes mellitus (diabetic kidney disease; DKD).
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus standard care.

**Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)**

Component	Description
Population	Patients with chronic kidney disease (present for $\geq 3$ months) and type 2 diabetes mellitus with eGFR $> 25$ mL/min/1.73 m <sup>2</sup> , and UACR $\geq 200$ mg/g.
Intervention	Finerenone 10 mg or 20 mg oral tablets once daily, in combination with standard of care (SoC).
Comparator	Placebo in combination with SoC, comprised of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB), <u>and a sodium-glucose cotransporter-2 inhibitor (SGLT2i) unless contraindicated.</u>
Outcomes	Composite outcome of onset of kidney failure, sustained decrease of eGFR $\geq 40\%$ from baseline over at least 4 weeks, or renal death. Composite outcome of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for heart failure.
Clinical claim	Finerenone is superior in terms of efficacy and <u>inferior in terms of safety</u> compared to placebo in combination with SoC.

Source: Table 13, p3 of the resubmission.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; SoC, standard of care; SGLT2i, sodium-glucose cotransporter-2 inhibitor; UACR, urinary albumin-creatinine ratio.

Note: Underlined text signifies key changes compared to previous submission.

### 2 Background

#### Registration status

- 2.1 Finerenone was approved by the TGA on 25 November 2021 for the following indication: ‘to delay progressive decline of kidney function in adults with chronic kidney disease associated with type 2 diabetes (with albuminuria), in addition to standard of care.’
- 2.2 The TGA decision for a proposed amendment to the finerenone indication was not available at the time of PBAC consideration. The proposed amendment to the indication is as follows: ‘to delay progressive decline of kidney function and to reduce the risk of cardiovascular mortality and morbidity in adults with chronic kidney disease associated with type 2 diabetes, in addition to standard of care.’ The TGA delegate’s file note (6 January 2023) stated that the overall clinical evidence from the FIDELO-

DKD and FIGARO-DKD trials supports the proposed Australian indication, but recommends further changes to the finerenone Product Information document, including the following: ‘treatment with finerenone was shown to have differential effect on non-fatal stroke with results indicative of beneficial effect in diabetic patients with history of cardiovascular disease but adverse effect in diabetic patients without history of cardiovascular disease’.

### Previous PBAC consideration

2.3 Table 2 (below) summarises the key matters of concern identified at the July 2022 PBAC meeting, and how these were addressed in the resubmission.

**Table 2: Summary of key matters of concern**

Matter of concern (July 2022 meeting)	Addressed in the resubmission
<b>Context and intended use</b>	
The PBAC considered that finerenone had a limited place in therapy in patients with very high albuminuria (UACR $\geq$ 300 mg/g), excluding HFrEF, as an add-on to standard of care comprising an ACEi or ARB and SGLT2i unless contraindicated (para 7.3, Finerenone PSD, July 2022 PBAC meeting).	The requested restriction was revised to include a UACR $\geq$ 200 mg/g, consistent with the dapagliflozin listing for CKD. The revised requested restriction also included a clinical criterion specifying that treatment must be in combination with an SGLT2i (unless medically contraindicated or intolerant).
The PBAC considered the nominated comparator (standard of care) was appropriate but was inconsistent with current clinical practice, and proposed a more restricted definition of standard of care comprising an ACEi or ARB and SGLT2i (unless contraindicated), in line with the more limited clinical position proposed (para 7.4, Finerenone PSD, July 2022 PBAC meeting).	The comparator was revised to be consistent with the place in therapy proposed by the PBAC; i.e. standard of care comprised of treatment with an ACEi or ARB in combination with an SGLT2i (unless contraindicated or intolerant).
<b>Clinical evidence</b>	
The PBAC considered that the magnitude of benefit for patients receiving an SGLT2i was highly uncertain due to a small number of patients in the clinical trials receiving this class of drug (para 7.7, Finerenone PSD, July 2022 PBAC meeting).	The resubmission presented additional <i>post hoc</i> subgroup (and complement) analyses from the FIGARO-DKD, FIDELIO-DKD and pooled FIDELITY analysis including: <ul style="list-style-type: none"> <li>• Baseline UACR <math>\geq</math> 200 mg/g.</li> <li>• Baseline UACR <math>\geq</math> 200 mg/g and SGLT2i use.</li> <li>• Baseline UACR <math>\geq</math> 200 mg/g and no SGLT2i use.</li> </ul>
The PBAC noted that the reduction in serious adverse events observed in patients treated with finerenone was partly driven by a reduction in complications associated with diabetic kidney disease, and that the risk of hyperkalaemia was likely to be greater outside the tightly controlled environment of a clinical trial. Therefore, the PBAC did not consider the claim of comparable safety to placebo was adequately supported (para 7.8, Finerenone PSD, July 2022 PBAC meeting).	The resubmission revised the clinical claim to finerenone has an inferior safety compared to placebo.
<b>Economic evaluation</b>	
The PBAC advised that the baseline risk in the economic model be adjusted to reflect the proposed PBS population, including use only in patients with very high albuminuria (UACR $\geq$ 300 mg/g), and expected use of concomitant SGLT2i therapy (para 7.10, Finerenone PSD, July 2022 PBAC Meeting).	Baseline patient characteristics were revised based on the FIDELITY UACR $\geq$ 200 mg/g subgroup. Baseline CKD, heart failure hospitalisation, cardiovascular mortality and hyperkalaemia risks were based on the FIDELITY UACR $\geq$ 200 mg/g SGLT2i non-user subgroup, adjusted for SGLT2i treatment effects (based on the results of the DAPA-CKD trial diabetes subgroup).

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<b>Matter of concern (July 2022 meeting)</b>	<b>Addressed in the resubmission</b>
<p>It was inappropriate for the submission to have assumed independent treatment effects for progression in chronic kidney disease and progression to dialysis, as both treatment effects share a high degree of overlap (the PBAC noted this was adjusted in the evaluation alternative base case in Table 16) (para 7.10, Finerenone PSD, July 2022 PBAC Meeting).</p>	<p>The resubmission argued that it was appropriate to apply independent finerenone treatment effects for progression to CKD stage 5 and progression to dialysis.</p> <p>The resubmission presented Kaplan Meier curves comparing time to dialysis in patients that reach CKD stage 5 for patients treated with finerenone versus placebo to support a treatment effect for finerenone in delaying progression to dialysis from CKD stage 5.</p> <p>In response to ESC advice (paragraph 6.46), the pre-PBAC response provided a revised economic model with equal rates of progression from CKD 5 to dialysis in both arms of the model (hazard ratio [HR] = 1).</p>
<p>Based on subgroup analyses in SGLT2i users/non-users presented in the July 2022 submission, the PBAC considered that the magnitude of treatment benefit for patients receiving an SGLT2i was highly uncertain due to the small number of patients in the clinical trials receiving this class of drugs (6.7% in FIDELITY), which resulted in imprecise and inconsistent results across the clinical trial subgroup analyses for this group. Given this uncertainty, the PBAC considered that conservative estimates of treatment effect in these patients would be most appropriate (para 7.7, Finerenone PSD, July 2022 PBAC meeting).</p>	<p>Based on the <i>post hoc</i> subgroup analyses presented in Section 2.6, the resubmission claimed that there is a comparable (if not greater) treatment effect in the FIDELITY UACR <math>\geq</math> 200 mg/g subgroup and UACR <math>\geq</math> 200 mg/g SGLT2i user subgroup relative to the FIDELITY whole study population, on composite cardiovascular and renal endpoints. The resubmission acknowledged the uncertainty in the UACR <math>\geq</math> 200 mg/g SGLT2i user subgroup, due to the small numbers of patients, and the treatment effect of finerenone was appropriately based on the FIDELITY whole study (FAS) population.</p>
<p>The PBAC considered that the modelled treatment effects of finerenone on the constructed composite endpoints for first non-fatal cardiovascular event and subsequent cardiovascular event were not adequately supported by the clinical trial data, which indicated a reduction in heart failure events, but not in myocardial infarction and stroke events (para 7.10 and Table 13, Finerenone PSD, July 2022 PBAC Meeting).</p>	<p>The model has been revised so that only first and subsequent heart failure hospitalisation events are modelled.</p>
<p>The model structure did not appropriately account for the relationship between renal disease progression, risk of hyperkalaemia, and treatment discontinuation, which should have been connected. The PBAC considered that treatment discontinuation and hyperkalaemia events in the extrapolated period did not reflect clinical practice where both hyperkalaemia and discontinuation become more likely as renal function impairment progresses (para 7.10, Finerenone PSD, July 2022 PBAC Meeting).</p>	<p>The revised economic evaluation applies risks of hyperkalaemia and hyperkalaemia-related discontinuation based on CKD stage in the model, which allows the risks of hyperkalaemia to increase with renal disease progression. However, finerenone treatment discontinuation is unchanged in the resubmission and assumed to be independent of CKD stage. Therefore, the ESC considered that this issue was only partly addressed in the resubmission (paragraph 6.42). In response to the ESC advice, the pre-PBAC response provided a revised economic model with increased treatment discontinuation probabilities (submission base case: CKD1/2 = 3.48%, CKD3 = 3.78%, CKD4 = 4.08%; pre-PBAC response: CKD5 = 4.63%; CKD1/2 = 3.48%, CKD3 = 4.12%, CKD4 = 4.76%, and CKD5 = 5.64%).</p>
<p>The costs applied to the dialysis health state were overestimated, and the costs applied in the evaluation alternative base case in Table 16 more accurately reflected current Australian practice (para 7.10, Finerenone PSD, July 2022 PBAC Meeting).</p>	<p>The revised model uses the same approach to costing dialysis as applied in the evaluation alternative base case. In addition, the AIHW total health price index was used to inflate all costs (if required) in the model to be consistent with the approach to the costing of dialysis.</p>

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<b>Matter of concern (July 2022 meeting)</b>	<b>Addressed in the resubmission</b>
The PBAC concluded that finerenone as an add-on to SoC including an SGLT2i, was unlikely to be cost-effective at a price greater than that accepted for dapagliflozin for CKD (para 7.9, Finerenone PSD, July 2022 PBAC Meeting).	The proposed DPMQ of finerenone was unchanged in the resubmission. The pre-PBAC response provided a price reduction from \$████ AEMP to \$████ AEMP.
<b>Utilisation and financial impact of listing</b>	
The PBAC considered that the financial estimates did not reflect the more limited clinical position proposed by PBAC for finerenone use following treatment with an ACEi/ARB and SGLT2i (unless contraindicated) and in patients with very high albuminuria (para 7.11, Finerenone PSD, July 2022 PBAC meeting).	A revised budget impact analysis is presented in the resubmission consistent with the sponsor's proposed revised PBS population.
The PBAC proposed an alternative approach for estimating the size of the eligible DKD population, and considered that the number of treated patients would be substantially lower than had been estimated in the submission (para 7.11, Finerenone PSD, July 2022 PBAC meeting).	The proposed PBAC approach was followed in the resubmission and supplemented with revised estimates. The size of the eligible and treated population was lower than what was proposed in the previous submission. The PBAC noted that the revised utilisation estimates did not include parameters previously accepted for dapagliflozin (Table 23, dapagliflozin PSD, November 2021). See paragraph 6.78.

Source: Table 12, p2, Table 23, pp27-28; Table 67, pp108-112, and Table 109, pp183-184 of the resubmission.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; DKD, diabetic kidney disease; DPMQ, dispensed price for maximum quantity; FAS, full analysis set; HFREF, heart failure with reduced ejection fraction; ICER, incremental cost-effectiveness ratio; PBAC, Pharmaceutical Benefits Advisory Committee; PSD, Public Summary Document; SGLT2i, sodium glucose co-transporter 2 inhibitor; UACR, urinary albumin-creatinine ratio.

For more detail on PBAC's view, see section 7 PBAC outcome.

### 3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

<b>MEDICINAL PRODUCT</b> medicinal product pack	<b>Dispensed Price for Max. Qty<sup>a</sup></b>	<b>PBS item code</b>	<b>Max. qty packs</b>	<b>Max. qty units</b>	<b>No. of Rpts</b>	<b>Available brands</b>
<b>FINERENONE</b>						
finerenone 10 mg tablet, 28	\$	NEW	1	28	5	Kerendia
finerenone 20 mg tablet, 28	\$	NEW	1	28	5	Kerendia
<b>Restriction Summary [new] / Treatment of Concept: [new]</b>						
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)						
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners						
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (Streamlined)						
<b>Administrative Advice:</b> <i>For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.</i>						
<b>Condition:</b> Chronic kidney disease with Type 2 diabetes						
<b>Indication:</b> Chronic kidney disease with Type 2 diabetes						
<b>Clinical criteria:</b>						
Patient must have a diagnosis of chronic diabetic kidney disease, defined as abnormalities of <i>at least one of:</i> (i) kidney structure, <del>or</del> (ii) kidney function, present for <i>at least 3 months or more</i> , prior to initiating treatment with this drug,						

<b>AND</b>
<b>Clinical criteria:</b>
Patient must not have known significant non-diabetic renal disease, prior to initiating treatment with this drug.
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have an estimated glomerular filtration rate of <del>greater than</del> 25 mL/min/1.73 m <sup>2</sup> or greater, prior to initiating treatment with this drug
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have a urinary albumin-to-creatinine ratio of <del>greater than</del> 200 mg/g (22.6 mg/mmol) or greater, <del>inclusive</del> prior to initiating treatment with this drug
<b>AND</b>
<b>Clinical criteria:</b>
Patient must discontinue treatment with this drug prior to initiating renal replacement therapy, defined as dialysis or kidney transplant,
<b>AND</b>
<b>Clinical criteria:</b>
Patient must be stabilised, for at least 4 weeks, on either: (i) an ACE inhibitor or (ii) an angiotensin II receptor antagonist, unless medically contraindicated, prior to initiation of combination therapy with this drug.
<b>AND</b>
<b>Clinical criteria:</b>
The treatment must be in combination with an SGLT2i unless medically contraindicated or intolerant.
<b>AND</b>
<b>Clinical criteria:</b>
Patient must not be receiving treatment with another selective nonsteroidal mineralocorticoid-receptor antagonist, a renin inhibitor or a potassium-sparing diuretic.
<b>AND</b>
<b>Clinical criteria:</b>
Patient must not have established heart failure with reduced ejection fraction with an indication for treatment with a mineralocorticoid receptor antagonist.
<b>Caution:</b>
<i>Serum electrolytes should be checked regularly</i>

<sup>a</sup> Represents price reduction (DPMQ) proposed in the pre-PBAC response

- 3.2 The proposed price, and flat pricing arrangement across the 10 mg and 20 mg dose strengths of finerenone were unchanged from the previous submission. However, the pre-PBAC response proposed a price reduction for finerenone from \$|AEMP (\$|DPMQ) to \$|AEMP (\$|DPMQ).
- 3.3 The requested restriction is narrower than the TGA indication but broadly consistent with the target population recommended by the PBAC at the July 2022 meeting: the PBAC previously considered that finerenone likely had a more limited place in therapy for use in patients with very high albuminuria (urinary albumin-to-creatinine ratio [UACR] of 300 mg/g [33.9 mg/mmol] or greater), excluding patients with heart failure with reduced ejection fraction (HFrEF), and as an add-on to standard of care comprising an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) and sodium-glucose cotransporter-2 inhibitor (SGLT2i) unless contraindicated (para 7.3, Finerenone Public Summary Document (PSD), July 2022

PBAC meeting). However, the proposed clinical criteria limit eligibility to patients exhibiting albuminuria consistent with moderate to severe kidney disease (UACR  $\geq 200$  mg/g), which is broadly consistent with the UACR criterion in the dapagliflozin CKD restriction, enabling patient's with a UACR of 200-299 mg/g access to both medicines. The ESC considered the clinical need for finerenone treatment in this patient group and the alignment between the finerenone and dapagliflozin restrictions was uncertain. The pre-PBAC response reiterated that finerenone demonstrated a significant treatment effect across cardiovascular and renal endpoints for the UACR  $\geq 200$  mg/g subgroups in the FIDELIO, FIGARO, and FIDELITY pooled analysis and that from a clinical management perspective, it would be practical to align the finerenone UACR cut-off to the dapagliflozin restriction.

- 3.4 The ESC agreed with the evaluation, that the omission of the caution recommended by the secretariat at the July 2022 meeting, 'serum electrolytes should be checked regularly' (para 3.1, Finerenone PSD, July 2022 PBAC meeting), was not adequately justified. Given the risk of hyperkalaemia observed for patients treated with finerenone versus placebo in the FIDELIO-DKD and FIGARO-DKD trials (see paragraphs 6.27-6.30), the ESC advised that the caution for ongoing electrolyte monitoring be included in the restriction.
- 3.5 The submission requested a Streamlined Authority PBS listing with general practitioner and nurse (for continuation scripts only) prescribing. Given the proposed population has been narrowed to patients with more severe diabetic kidney disease, initiation of finerenone by specialists may be appropriate and more consistent with Australian guidelines for patients with CKD (KHA 2020).

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **4 Population and disease**

- 4.1 Type 2 diabetes (T2D) is a common chronic illness characterised by high blood glucose levels due to inadequate insulin production and/or inadequate cellular response to insulin. CKD is a broad collection of diseases resulting in a decreased eGFR and/or leakage of protein or albumin into the urine. The diagnosis and staging of CKD are typically defined by the eGFR and the magnitude of albuminuria. T2D, CKD and cardiovascular disease are interrelated comorbidities, with diagnosis of each disease associated with an increased baseline risk of developing each comorbidity, as well as increased overall burden of disease. Diabetic kidney disease is diagnosed when CKD is comorbid with T2D, with or without comorbid cardiovascular disease.
- 4.2 Finerenone is a non-steroidal mineralocorticoid receptor antagonist (MRA) and belongs to a broad group of potassium-sparing diuretics (spironolactone, eplerenone), that work by inhibiting mineralocorticoid receptor-mediated sodium reabsorption as well as mineralocorticoid receptor overactivation which may contribute to fibrosis and inflammation in both epithelial and nonepithelial tissues.

- 4.3 Finerenone is administered as a 10 mg or 20 mg oral tablet once daily, and is intended to be used as a chronic ongoing therapy. Co-administered therapies given in combination with finerenone include medicines prescribed as standard of care (SoC) for diabetic kidney disease (ACEi, ARB, SGLT2i medicines), and other CKD and T2D medicines. The product information states that finerenone should not be used in combination with other MRA medicines or potassium-sparing diuretics (e.g. spironolactone, eplerenone, amiloride, triamterene).

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **5 Comparator**

- 5.1 The resubmission nominated standard of care as the main comparator, comprised of treatment with an ACEi or ARB in combination with an SGLT2i therapy (unless contraindicated or intolerant). This is consistent with the comparator suggested by the PBAC for finerenone in the more limited role identified at the July 2022 meeting (para 7.4, Finerenone PSD, July 2022 PBAC meeting). The ESC advised that the nominated comparator was appropriate.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the burden of disease, the mechanism of action of finerenone, outlined the pivotal clinical trials, and how finerenone would be used in clinical practice. The clinician stated that finerenone was complimentary to current standard of care medications (ACE inhibitor or ARB and SGLT2i) and highlighted that clinical benefit was consistent irrespective of SGLT2i use. The clinician also outlined the rates of hyperkalaemia reported in the clinical trials and considered that the protocols utilised in the clinical trials to reduce the risk of hyperkalaemia would be manageable in clinical practice. The PBAC noted the hearing was aligned with the evidence presented in the resubmission.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from 1 organisation (Kidney Health Australia) via the Consumer Comments facility on the PBS website. The statement provided by the organisation noted the benefits of treatment with finerenone, including its potential to slow disease progression and also provide a treatment option for patients who cannot tolerate renin angiotensin aldosterone system inhibitors (RAASi) or SGLT2is. The statement also acknowledged the main disadvantages for patients would relate to pill burden and potential side effects (in particular hyperkalaemia). The PBAC noted the comments were supportive of the evidence presented in the resubmission.

**Clinical trials**

- 6.3 The resubmission was based on two head-to-head randomised trials comparing finerenone to placebo in patients with diabetic kidney disease (FIDELIO-DKD, FIGARO-DKD), and a pre-specified pooled analysis of individual patient data from these trials (FIDELITY). This is unchanged from the July 2022 submission.
- 6.4 In addition, the resubmission presented new *post hoc* subgroup analyses of the FIDELITY pooled data study, of patients with a UACR > 200 mg/g, with or without concomitant treatment with an SGLT2i medicine, and the incidence hyperkalaemia by baseline UACR and eGFR.
- 6.5 Details of the trials presented in the submission are provided in Table 3.

**Table 3: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
FIDELIO-DKD	<p>Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and Diabetic Kidney Disease</p> <p>Bakris et al. Design and baseline characteristics of the finerenone in reducing kidney failure and disease progression in diabetic kidney disease trial.</p> <p>Bakris et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes.</p> <p>Filippatos et al. Finerenone and Cardiovascular Outcomes in Patients with Chronic Kidney Disease and Type 2 Diabetes.</p> <p>Filippatos et al. Finerenone Reduces New-Onset Atrial Fibrillation in Patients With Chronic Kidney Disease and Type 2 Diabetes.</p> <p>Agarwal et al. Hyperkalemia Risk with finerenone: Results from the FIDELIO-DKD Trial.</p> <p>Rossing et al. Finerenone in Predominantly Advanced CKD and Type 2 Diabetes With or Without Sodium-Glucose Cotransporter-2 Inhibitor Therapy.</p> <p>Filippatos et al. Finerenone in patients with CKD and T2D with and without heart failure: A prespecified subgroup analysis of the FIDELIO-DKD trial.</p> <p>Rossing et al. Finerenone in Patients With Chronic Kidney Disease and Type 2 Diabetes According to Baseline HbA1c and Insulin Use: An Analysis From the FIDELIO-DKD Study.</p> <p>Rossing et al. Efficacy and safety of finerenone in patients with chronic kidney disease and type 2 diabetes by GLP1RA treatment: A subgroup analysis from the FIDELIO-DKD trial.</p>	<p>Internal study report: 2020.</p> <p><i>American Journal of Nephrology</i>. 2019, 50(5):333-345.</p> <p><i>New England Journal of Medicine</i>. 2020, 383(23):2219-2229.</p> <p><i>Circulation</i>. 2021, (143):540-552.</p> <p><i>Journal of the American College of Cardiology</i>. 2021b, (78):142-152.</p> <p><i>Journal of the American Society of Nephrology</i>. 2022, (33):225–237.</p> <p><i>Kidney International Reports</i>. 2021, (7): 36-45.</p> <p><i>European Journal of Heart Failure</i>. 2022, 24(6):996-1005.</p> <p><i>Diabetes Care</i>. 2022, 45(12):888-897.</p> <p><i>Diabetes, Obesity &amp; Metabolism</i>. 2022b, (24):125-134.</p>
FIGARO-DKD	<p>Efficacy and safety of finerenone in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic kidney disease.</p> <p>Ruilope et al. Design and baseline characteristics of the finerenone in reducing cardiovascular mortality and morbidity in diabetic kidney disease trial.</p> <p>Pitt et al. Cardiovascular events with finerenone in kidney disease and Type 2 diabetes.</p> <p>Filippatos et al. Finerenone reduces risk of incident heart failure in patients with chronic kidney disease and Type 2 diabetes: analyses from the FIGARO-DKD trial.</p>	<p>Internal study report: 2021.</p> <p><i>American Journal of Nephrology</i>. 2019, 50:345-356.</p> <p><i>New England Journal of Medicine</i>. 2021, 385:2252-2263.</p> <p><i>Circulation</i>. 2022, 145: 437-447.</p>
FIDELITY	<p>Bayer. Integrated analysis of FIDELIO-DKD and FIGARO-DKD.</p> <p>Agawal et al. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis.</p> <p>Rossing et al. Finerenone in Patients With Chronic Kidney Disease and type 2 Diabetes by Sodium-Glucose Cotransporter 2 Inhibitor Treatment: The FIDELITY Analysis.</p>	<p>Internal study report: 2021.</p> <p><i>European Heart Journal</i>. 2022, 43: 474-484.</p> <p><i>Diabetes Care</i>. 2022, 45(12):2991-2998.</p>

Source: Table 26, p33-35 of the resubmission; Section 2.2.1, p31-32 of the resubmission.

Note: Abstracts of studies with full publications are not presented.

6.6 The key features of the included trials are summarised in Table 4.

**Table 4: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
FIDELIO-DKD	5,734	MC, R, DB, PC Event-driven trial Mean 32 month duration	Low	Patients with diabetic kidney disease (predominantly advanced disease) receiving ACEi or ARB monotherapy as part of standard of care	Cardiorenal outcomes, biomarkers, quality of life and adverse events	Not used
FIGARO-DKD	7,437	MC, R, DB, PC Event-driven trial Mean 40 month duration	Low	Patients with diabetic kidney disease receiving ACEi or ARB monotherapy as part of standard of care	Cardiorenal outcomes, biomarkers, quality of life and adverse events	Not used
FIDELITY	13,026	Pooled analysis of individual patient data from FIDELIO-DKD and FIGARO-DKD	Low	Patients with diabetic kidney disease receiving ACEi or ARB monotherapy as part of standard of care	Cardiorenal outcomes, biomarkers, quality of life and adverse events	Baseline risk, treatment effects, utility values

Source: Section 2.3, pp40-43 of the resubmission.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; DB, double-blind; MC, multicentre; PC, placebo-controlled; R, randomised.

- 6.7 The FIDELIO-DKD and FIGARO-DKD trials included predominantly older, white or Asian, male populations with a history of diabetes (mean 15 years duration of diabetes), established chronic kidney disease (baseline mean eGFR 57 mL/min/1.73 m<sup>2</sup>; median UACR 515 mg/g) and related comorbidities, excluding HFrEF, non-diabetic renal disease and other conditions requiring treatment with mineralocorticoid receptor antagonists, renin inhibitors or potassium-sparing diuretics. The FIDELIO-DKD trial population was generally at higher risk of complications compared to the FIGARO-DKD trial (83.4% vs. 21.1% at very high risk; KDIGO criteria).
- 6.8 Both trials used a quota-based sampling approach which limited the proportions of patients with particular characteristics (e.g. very high albuminuria with eGFR ≥ 60 to <75 mL/min/1.73 m<sup>2</sup>, high albuminuria with diabetic retinopathy, high albuminuria with eGFR ≥ 60 mL/min/1.73 m<sup>2</sup>, high albuminuria without cardiovascular disease). These artificial constraints distorted the distribution of patients across the diabetic kidney disease spectrum as well as the underlying risk of cardiorenal events in the trials, and are not representative of clinical practice.
- 6.9 At the July 2022 meeting the PBAC noted that the management of hyperkalaemia in clinical practice could lead to suboptimal finerenone dosing in the Australian setting, given the risk of hyperkalaemia in the clinical trials was managed by careful patient selection, intensive monitoring, finerenone dose titration/interruption, and the use of potassium lowering agents. In addition, while the majority of patients in the clinical

trials were using the higher 20 mg finerenone dose strength, the ESC had previously considered it was unclear if treating physicians would avoid up titration to the higher dose due to concerns over the risk of hyperkalaemia (para 6.11, Finerenone PSD, July 2022 PBAC meeting).

- 6.10 The resubmission noted that the risk of hyperkalaemia in the Australian setting is managed at the discretion of treating physicians, and that a commissioned panel of Australian based nephrologists and endocrinologists advised that for patients with CKD, serum potassium measurement occurs every 3-6 months, comparable to the clinical trials where serum potassium measurement occurred every 4 months. No documentation of the expert advice was provided in the resubmission.
- 6.11 The resubmission also noted the high rate of patients never dispensed finerenone 20 mg in the FIDELITY pooled analysis (59.3%) and suggested it was unlikely there would be lower rates of finerenone 20 mg dosing in the Australian setting. The resubmission's estimate appears to be based on patients who were not dispensed finerenone 20 mg on at least one visit and is inconsistent with exposure data indicating that the majority of patients received finerenone 20 mg in both trials.
- 6.12 Both trials were conducted prior to recent guideline recommendations for the use of SGLT2i medicines and GLP1 analogues to reduce the risk of cardiovascular and renal complications in patients with diabetic kidney disease, and the use of these therapies in the trials was very low and unlikely to represent clinical practice.

### ***Comparative effectiveness***

- 6.13 The results of the FIDELIO-DKD and FIGARO-DKD trials and FIDELITY pooled analyses presented in the resubmission are unchanged from the July 2022 finerenone submission, and are presented below for completeness.
- 6.14 The composite cardiovascular (primary outcome in FIGARO-DKD; key secondary outcome in FIDELIO-DKD) and renal events (primary outcome in FIDELIO-DKD; key secondary outcome in FIGARO-DKD) reported in the FIDELIO-DKD and FIGARO-DKD trials are summarised in Table 5 below.

Table 5: Composite cardiovascular and renal events in FIDELIO-DKD and FIGARO-DKD (FAS)

Outcome	Finerenone n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)
<b>Composite cardiovascular events<sup>a</sup></b>			
FIDELIO-DKD	367/2,833 (13.0%)	420/2,841 (14.8%)	<b>0.86 (0.75, 0.99)</b>
FIGARO-DKD (primary outcome)	458/3,686 (12.4%)	519/3,666 (14.2%)	<b>0.87 (0.76, 0.98)</b>
FIDELITY pooled analysis	825 (12.7%)	939 (14.4%)	<b>0.86 (0.78, 0.95)</b>
<b>Composite renal events (including ≥ 40% decrease in eGFR)<sup>b</sup></b>			
FIDELIO-DKD (primary outcome)	504/2,833 (17.8%)	600/2,841 (21.1%)	<b>0.83 (0.73, 0.93)</b>
FIGARO-DKD	350/3,686 (9.5%)	395/3,666 (10.8%)	0.87 (0.76, 1.01)
FIDELITY pooled analysis	854 (13.1%)	995 (15.3%)	<b>0.85 (0.77, 0.93)</b>
<b>Composite renal events (including ≥ 57% decrease in eGFR)<sup>c</sup></b>			
FIDELIO-DKD (primary outcome)	252/2,833 (8.9%)	326/2,841 (11.5%)	0.76 (0.65, 0.90)
FIGARO-DKD	108/3,686 (2.9%)	139/3,666 (3.8%)	0.77 (0.60, 0.99)
FIDELITY pooled analysis	360 (5.5%)	465 (7.1%)	<b>0.77 (0.67, 0.88)</b>

Source: Table 39, p63, Table 40, p64, Table 41, p65, Table 47, p72, and Table 48, p73 of the resubmission.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set.

<sup>a</sup> Composite of the time to cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation due to heart failure.

<sup>b</sup> Composite of the time to kidney failure, sustained decrease of eGFR greater or equal to 40% from baseline over at least 4 weeks, or renal death.

<sup>c</sup> Composite of the time to kidney failure, sustained decrease of eGFR greater or equal to 57% from baseline over at least 4 weeks, or renal death.

Note: Result in bold are statistically significant.

- 6.15 Treatment with finerenone was associated with statistically significant reductions in cardiovascular events compared to placebo and renal composite outcomes (using both the 40% and 57% eGFR thresholds) in the pooled analysis.
- 6.16 Exploratory analyses of individual outcomes suggested that treatment with finerenone was associated with reductions in heart failure hospitalisation, worsening renal impairment and progression to kidney failure.
- 6.17 Further exploratory analyses of cardiovascular mortality indicate that while finerenone was not associated with a statistically significant reduction in the broader category of cardiovascular death it may be associated with a reduction in sudden cardiac death and death due to heart failure. However, further analyses of myocardial infarction and stroke exploratory outcomes did not clearly demonstrate a reduction in risk with finerenone treatment.
- 6.18 There were no major differences in quality of life scores (EQ-5D-5L and Kidney Disease Quality of Life, KDQOL-36) between finerenone and placebo treatment arms.
- 6.19 The pre-specified subgroup analyses of cardiovascular outcomes did not suggest any major treatment effect interactions.
- 6.20 The pre-specified subgroup analyses of renal outcomes strongly suggested that baseline BMI was a treatment effect modifier. The subgroup analyses also suggested treatment effect interactions by region, race, albuminuria and baseline potassium.
- 6.21 The composite cardiovascular and renal events reported in the FIDELITY *post hoc* subgroup analyses (baseline UACR ≥ 200 mg/g with and without SGLT2i use) are summarised in Table 6 below.

**Table 6: Composite cardiovascular and renal events in the FIDELITY pooled data *post hoc* subgroup analyses (baseline UACR ≥ 200 mg/g with and without SGLT2i use; FAS)**

	Patients with composite events n/N (%)		Composite events per 100 patient years (95% CI)		Hazard ratio (95%CI)
	Finerenone	Placebo	Finerenone	Placebo	
<b>Composite cardiovascular events<sup>a</sup></b>					
FIDELITY (FAS) <sup>b</sup>	825/6519 (12.7%)	939/6507 (14.4%)	4.34 (4.05; 4.64)	5.01 (4.69; 5.33)	<b>0.86 (0.78, 0.95)</b>
UACR ≥ 200 mg/g	623/4879 (12.8%)	700/4871 (14.4%)	4.63 (4.27; 5.00)	5.27 (4.89; 5.67)	<b>0.88 (0.79, 0.98)</b>
UACR ≥ 200 mg/g + baseline SGLT2i	29/324 (9.0%)	41/324 (12.7%)	3.18 (2.13; 4.44)	4.72 (3.39; 6.27)	0.70 (0.42, 1.17)
UACR ≥ 200 mg/g no baseline SGLT2i	594/4555 (13.0%)	659/4547 (14.5%)	4.73 (4.36; 5.12)	5.31 (4.91; 5.72)	<b>0.89 (0.79, 0.99)</b>
<b>Composite renal events (including ≥ 40% decrease in eGFR)<sup>c</sup></b>					
FIDELITY (FAS) <sup>b</sup>	854/6519 (13.1%)	995/6507 (15.3%)	4.81 (4.49; 5.14)	5.64 (5.29; 5.99)	<b>0.85 (0.77, 0.93)</b>
UACR ≥ 200 mg/g	730/4879 (15.0%)	889/4871 (18.3%)	5.84 (5.43; 6.28)	7.14 (6.68; 7.62)	<b>0.81 (0.74, 0.90)</b>
UACR ≥ 200 mg/g + baseline SGLT2i	27/324 (8.3%)	28/324 (8.6%)	3.08 (2.03; 4.35)	3.36 (2.23; 4.71)	0.68 (0.38, 1.24)
UACR ≥ 200 mg/g no baseline SGLT2i	703/4555 (15.4%)	861/4547 (18.9%)	6.05 (5.61; 6.51)	7.42 (6.93; 7.92)	<b>0.82 (0.74, 0.90)</b>
<b>Composite renal events (including ≥ 57% decrease in eGFR)<sup>d</sup></b>					
FIDELITY (FAS) <sup>b</sup>	360/6519 (5.5%)	465/6507 (7.1%)	1.96 (1.77; 2.17)	2.55 (2.33; 2.79)	<b>0.77 (0.67, 0.88)</b>
UACR ≥ 200 mg/g	331/4879 (6.8%)	442/4871 (9.1%)	2.56 (2.29; 2.84)	3.42 (3.11; 3.75)	<b>0.75 (0.65, 0.86)</b>
UACR ≥ 200 mg/g + baseline SGLT2i	7/324 (2.2%)	17/324 (5.2%)	0.78 (0.32; 1.46)	2.00 (1.16; 3.05)	<b>0.33 (0.13, 0.87)</b>
UACR ≥ 200 mg/g no baseline SGLT2i	324/4555 (7.1%)	425/4547 (9.3%)	2.69 (2.40; 2.99)	3.52 (3.20; 3.87)	<b>0.77 (0.67, 0.89)</b>

Source: Table 54, p81, Table 56, p84, and Table 57, p86 of the resubmission.

Abbreviations: CI, confidence interval; CV, cardiovascular; FAS, full analysis set; SGLT2i, sodium-glucose cotransporter 2 inhibitor; UACR, urine albumin-creatinine ratio.

<sup>a</sup> Composite of the time to cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation due to heart failure

<sup>b</sup> Previously considered by the PBAC.

<sup>c</sup> Composite of the time to kidney failure, sustained decrease of eGFR greater or equal to 40% from baseline over at least 4 weeks, or renal death.

<sup>d</sup> Composite of the time to kidney failure, sustained decrease of eGFR greater or equal to 57% from baseline over at least 4 weeks, or renal death.

Note: Result in bold statistically significant.

- 6.22 The results for the cardiovascular and renal (40% or 57% eGFR threshold) composite outcomes in the FIDELITY *post hoc* subgroups with baseline UACR ≥ 200 mg/g with or without SGLT2i use, were generally consistent with the overall FIDELITY pooled population.
- 6.23 Given the small number of patients in the FIDELITY subgroup with baseline UACR ≥ 200 mg/g and SGLT2i use (n=324 in each treatment arm), and the small numbers of events, the results for the *post hoc* subgroup analyses should be interpreted with caution.
- 6.24 The *post hoc* subgroup with baseline UACR ≥ 200 mg/g and SGLT2i use showed a lower baseline risk of composite cardiovascular and non-fatal cardiovascular events and renal events compared to the overall FIDELITY pooled population and the *post hoc* subgroup with UACR ≥ 200 mg/g.

## Comparative harms

6.25 Table 7 summarises the adverse events reported in the FIDELIO-DKD and FIGARO-DKD trials.

**Table 7: Overall summary of adverse events in the included studies**

Treatment emergent adverse events	FIDELIO-DKD (mean 32 month treatment duration)		FIGARO-DKD (mean 40 month treatment duration)	
	Finerenone N = 2,827	Placebo N = 2,831	Finerenone N = 3,683	Placebo N = 3,658
Any adverse event	2,468 (87.3%)	2,478 (87.5%)	3,134 (85.1%)	3,129 (85.5%)
Treatment-related adverse event	646 (22.9%)	449 (15.9%)	560 (15.2%)	413 (11.3%)
Serious adverse event	902 (31.9%)	971 (34.3%)	1,158 (31.4%)	1,215 (33.2%)
Adverse events leading to discontinuation	207 (7.3%)	168 (5.9%)	207 (5.6%)	183 (5.0%)
Adverse events leading to death	31 (1.1%)	51 (1.8%)	79 (2.1%)	100 (2.7%)
<b>Adverse events of interest</b>				
Hyperkalaemia	516 (18.3%)	255 (9.0%)	396 (10.8%)	193 (5.3%)
Hyperkalaemia leading to hospitalisation	40 (1.4%)	8 (0.3%)	21 (0.6%)	2 (<0.1%)
Acute kidney injury <sup>a</sup>	129 (4.6%)	136 (4.8%)	91 (2.5%)	98 (2.7%)
Decreased glomerular filtration rate	179 (6.3%)	133 (4.7%)	169 (4.6%)	141 (3.9%)

Source: Table 44, p69, Table 45, p70 and Table 46, p71 of the resubmission; Table 10-22, p175 of the FIDELIO-DKD CSR; Table 10-2, p201 of the FIGARO-DKD CSR.

Abbreviations: eGFR, estimated glomerular filtration rate; TEAE, treatment emergent adverse events.

<sup>a</sup> Patients with treatment-emergent worsening of renal function or eGFR laboratory values, and any worsening of renal function TEAE leading to hospitalisation or permanent discontinuation of study drug.

Note: Hyperkalaemia: serum potassium > 5.5 mmol/L.

- 6.26 Treatment with finerenone was associated with an increased incidence of treatment-related adverse events and adverse events leading to discontinuation compared to placebo. Adverse events occurring more frequently in the finerenone arm included hyperkalaemia, decreased glomerular filtration rate, hypotension, hyperuricaemia, pruritis and increased blood potassium.
- 6.27 Hyperkalaemia was reported more frequently in patients treated with finerenone and finerenone treatment was associated with a decreased incidence of serious adverse events compared to placebo primarily due to a reduction in pneumonia and complications associated with underlying disease. At the July 2022 meeting, the PBAC considered that the reduction in serious adverse events was partly driven by a reduction in complications associated with diabetic kidney disease, and that the risk of hyperkalaemia was likely to be greater outside the tightly controlled environment of a clinical trial (paras 6.31 and 7.8, Finerenone PSD, July 2022 PBAC meeting).
- 6.28 In the subgroup with baseline UACR  $\geq$  200 mg/g and SGLT2i use, treatment with finerenone was associated with an increased incidence of treatment-related adverse events, hyperkalaemia and drug related hyperkalaemia compared to placebo, and were generally consistent with the overall FIDELITY pooled population (Table 8 and Table 9). However, there were smaller proportions of patients with hyperkalaemia

related adverse events in the *post hoc* subgroup with UACR  $\geq$  200 mg/g and SGLT2i use, compared to the overall FIDELITY pooled population.

**Table 8: Summary of key adverse events in the FIDELITY pooled analysis post hoc subgroup (baseline UACR  $\geq$  200 mg/g and SGLT2i use; SAS)**

Baseline characteristic	FIDELITY (FAS)		FIDELITY post hoc subgroup			
	Finerenone N = 6,510	Placebo N = 6,489	UACR $\geq$ 200 mg/g +SGLT2i		Complement	
			Finerenone N = 324	Placebo N = 324	Finerenone N = 6,186	Placebo N = 6,165
Any adverse event	5,602 (86.1%)	5,607 (86.4%)	290 (89.5%)	277 (85.5%)	5,312 (85.9%)	5,330 (86.5%)
Treatment related adverse events	1,206 (18.5%)	862 (13.3%)	51 (15.7%)	27 (8.3%)	1155 (18.7%)	835 (13.5%)
Adverse events leading to discontinuation	414 (6.4%)	351 (5.4%)	13 (4.0%)	15 (4.6%)	401 (6.5%)	336 (5.5%)
Serious adverse events	2,060 (31.6%)	2,186 (33.7%)	101 (31.2%)	94 (29.0%)	1,959 (31.7%)	2,092 (33.9%)
Treatment related serious adverse events	83 (1.3%)	61 (0.9%)	2 (0.6%)	0	81 (1.3%)	61 (1.0%)
Serious adverse events leading to discontinuation	145 (2.2%)	154 (2.4%)	5 (1.5%)	4 (1.2%)	140 (2.3%)	150 (2.4%)

Source: Table 51, p77, and Table 59, p89 of the resubmission.

Abbreviations: FAS, full analysis set; SAS, safety analysis set; SGLT2i, sodium glucose co-transporter 2 inhibitor; UACR, urinary albumin-creatinine ratio.

**Table 9: Summary of hyperkalaemia related adverse events in the FIDELITY pooled analysis post hoc subgroup (baseline UACR  $\geq$  200 mg/g and SGLT2i use), and complement**

Baseline characteristic	FIDELITY (FAS)		FIDELITY post hoc subgroup			
	Finerenone N = 6,519	Placebo N = 6,507	UACR $\geq$ 200 mg/g +SGLT2i		Complement	
			Finerenone N = 324	Placebo N = 324	Finerenone N = 6,195	Placebo N = 6,183
Investigator-reported hyperkalaemia	912 (14.0%)	448 (6.9%)	32 (9.9%)	6 (1.9%)	880 (14.2%)	442 (7.2%)
Drug related hyperkalaemia	573 (8.8%)	249 (3.8%)	18 (5.6%)	3 (0.9%)	555 (9.0%)	246 (4.0%)
Permanent discontinuation due to hyperkalaemia	110 (1.7%)	38 (0.6%)	3 (0.9%)	2 (0.6%)	107 (1.7%)	36 (0.6%)
Serious hyperkalaemia	69 (1.1%)	16 (0.2%)	1 (0.3%)	0	68 (1.1%)	16 (0.3%)
Drug-related serious hyperkalaemia	43 (0.7%)	8 (0.1%)	1 (0.3%)	0	42 (0.7%)	8 (0.1%)
Serious hyperkalaemia leading to discontinuation	NR	NR	1 (0.3%)	0	9 (0.1%)	2 (<0.1%)
Serious hyperkalaemia leading to hospitalisation	61 (0.9%)	10 (0.2%)	1 (0.3%)	0	60 (1.0%)	10 (0.2%)
Fatal serious hyperkalaemia	0	0	0	0	0 <sup>a</sup>	0 <sup>a</sup>

Source: Table 53, p79 and Table 60, pp91-92 of the resubmission.

Abbreviations: FAS, full analysis set; NR, not reported; SGLT2i, sodium glucose co-transporter 2 inhibitor; UACR, urinary albumin-creatinine ratio.

<sup>a</sup> Fatal serious hyperkalaemia events attributed to the post hoc subgroup complement (finerenone n=4, <0.1%; placebo n=5, <0.1%), reported in error, reported in Table 3/6 of 'Additional subgroup analyses.doc' as life threatening serious hyperkalaemia adverse events.

6.29 The results of the *post hoc* subgroup analysis of hyperkalaemia outcomes by eGFR show that lower baseline eGFR was associated with a higher incidence of hyperkalaemia, with larger proportions of patients treated with finerenone experiencing hyperkalaemia compared to placebo.

6.30 Results of the *post hoc* subgroup analysis of hyperkalaemia outcomes by UACR show smaller proportions of patients in both treatment arms experienced drug-related

hyperkalaemia in the subgroup with baseline UACR  $\geq$  200 mg/g and SGLT2i use compared to the overall FIDELITY pooled population and other subgroups (Table 10).

**Table 10: Hyperkalaemia events by baseline UACR subgroups in FIDELITY (post hoc analyses; SAS)**

	FIDELITY	
	Finerenone n/N (%)	Placebo n/N (%)
<b>Drug-related hyperkalaemia</b>		
Overall	573/6,510 (8.8%)	249/6,489 (3.8%)
Baseline UACR $\geq$ 200 mg/g	429/4,873 (8.8%)	193/4,860 (4.0%)
Complement	144/1,637 (8.8%)	56/1,629 (3.4%)
Baseline UACR $\geq$ 200 mg/g +SGLT2i	18/324 (5.6%)	3/324 (0.9%)
Complement	555/6,186 (9.0%)	246/6,165 (4.0%)
<b>Serious hyperkalaemia leading to hospitalisation</b>		
Overall	61/6,519 (0.9%)	10/6,507 (0.2%)
Baseline UACR $\geq$ 200 mg/g	45/4,873 (0.9%)	8/4,860 (0.2%)
Complement	16/1,637 (1.0%)	2/1,629 (0.1%)
Baseline UACR $\geq$ 200 mg/g +SGLT2i	1/324 (0.3%)	0
Complement	60/6,186 (1.0%)	10/6,165 (0.2%)
<b>Serious hyperkalaemia leading to discontinuation</b>		
Overall	10/6,519 (0.2%)	2/6,507 (<0.1%)
Baseline UACR $\geq$ 200 mg/g	7/4,873 (0.1%)	2/4,860 (<0.1%)
Complement	3/1,637 (0.2%)	0
Baseline UACR $\geq$ 200 mg/g +SGLT2i	1/324 (0.3%)	0
Complement	9/6,186 (0.1%)	2/6,165 (<0.1%)

Source: Tables 61, pp94-95 of the resubmission.

Abbreviations: SAS, safety analysis set; SGLT2i, sodium glucose co-transporter 2 inhibitor; UACR, urinary albumin-creatinine ratio.

Note: Hyperkalaemia: serum potassium > 5.5 mmol/L. Severe hyperkalaemia: serum potassium > 6.0 mmol/L.

## Benefits/harms

6.31 Based on the FIDELITY analysis, for every 1,000 patients treated with finerenone in comparison with placebo over 3 years:

- There would be 17 fewer cardiovascular events (primarily hospitalisation for heart failure).
- There would be 22 fewer renal events (primarily sustained worsening of kidney function).
- There would be 71 additional patients experiencing a hyperkalaemia event with 7 requiring hospitalisation.

6.32 Benefits and harms were not presented for the *post hoc* FIDELITY subgroup with baseline UACR  $\geq$  200 mg/g and SGLT2i use, given the small number of patients in the subgroup, and the small numbers of events.

## Clinical claim

6.33 The resubmission described finerenone as superior in terms of effectiveness and inferior in terms of safety compared to standard of care. The ESC considered these claims appeared reasonable based on the data presented in the resubmission.

6.34 The resubmission noted that the hyperkalaemia risk associated with finerenone can be managed by routine clinical monitoring. However, the finerenone trials managed

the risk of hyperkalaemia through a combination of careful patient selection, intensive monitoring and dose adjustments (down-titrations and dose interruptions) as well as increased use of potassium lowering agents. The PBAC previously considered that the risk of hyperkalaemia was likely to be greater outside the tightly controlled clinical trial environment (para 6.31, Finerenone PSD, July PBAC meeting). The Pre-Sub-Committee Response (PSCR) highlighted that the concomitant use of finerenone with a SGLT2i appears to offer some protection against hyperkalemic events compared with treatment without a SGLT2i in the pivotal trials. However, the ESC noted the small patient numbers in the UACR  $\geq 200$  mg/g and SGLT2i use subgroup and considered there was limited evidence to suggest that the risk of hyperkalaemia differed for the SGLT2i use subgroup patient population compared with the overall patient population. The PSCR also reiterated that the product information (PI) for finerenone outlines protocols for patient selection, monitoring and management of hyperkalaemia and argued that ESC previously considered that Australian physicians are well versed in the monitoring and management of hyperkalaemia (para 6.51, finerenone ESC Advice, July 2022 PBAC submission). The ESC considered that the finerenone patient population remain at an increased risk of hyperkalaemia compared with placebo and the risk of hyperkalaemia outside a controlled clinical trial environment was unknown. The ESC also considered it remained unclear whether physicians would up titrate to the higher finerenone dose in clinical practice due to concerns over the risk of hyperkalaemia and whether suboptimal dosing of finerenone may result. The pre-PBAC response argued that potassium management in the clinical trial was at the discretion of the physician and therefore likely aligns with real world clinical management. Furthermore, based on exposure data between July 2021 and July 2022 (17,649 patient years) the cumulative rate of hyperkalaemia related AEs was lower than the rates reported in the FIDELITY pooled analysis (0.25 per 100 patient years versus 5.84 per 100 patient years).

- 6.35 The PBAC considered that the claim of superior comparative effectiveness was reasonable.
- 6.36 The PBAC considered that the claim of inferior comparative safety was reasonable.

### ***Economic analysis***

- 6.37 The resubmission presented a stepped economic evaluation of finerenone compared to placebo for the treatment of patients with diabetic kidney disease with high/very high albuminuria and SGLT2i use, unless contraindicated or intolerant. The economic evaluation was based on the pooled FIDELITY analysis, with additional modelled data. The economic evaluation was presented as a cost-utility/cost-effectiveness analysis.
- 6.38 Compared with the July 2022 submission, the main changes to the economic evaluation include:
- Updated baseline patient characteristics and baseline risks to reflect the proposed place in therapy.

- The risk of transplant in dialysis patients is based on Australian data (ANZDATA 2020), rather than the FIDELITY pooled analysis.
- Only heart failure hospitalisation events are modelled, compared with a composite of myocardial infarction, stroke and heart failure hospitalisation events in the previous submission, reflected in updates to first and subsequent heart failure hospitalisation baseline risks, treatment effects, costs and utilities.
- Hyperkalaemia risks have been estimated by CKD stage, compared with the July 2022 submission which estimated hyperkalaemia risks independently of CKD stage. Discontinuations due to hyperkalaemia events have been added.
- Finerenone treatment adherence of 91.74% has been included (perfect adherence was assumed in the July 2022 submission) for consistency with the budget impact model.
- Dialysis costs have been revised to remove double counting of costs for dialysis surgery.
- SGLT2i use has been updated from 10.2% to 94.5% to reflect concomitant use.
- Where required, costs have been inflated using the AIHW Total Health Price Index instead of the CPI used in the July 2022 submission.

6.39 Table 11 presents the key components of the economic evaluation.

**Table 11: Key components of the economic evaluation**

Component	Description
Treatments	Finerenone; placebo.
Time horizon	15 years.
Outcomes	Patients free of renal failure and/or cardiovascular events; quality adjusted life years.
Methods used to generate results	Markov state-transition cohort model.
Health states	24 health states based on severity of kidney disease (CKD 1/2, CKD 3, CKD 4, CKD 5, acute/chronic dialysis, acute/chronic transplantation), the presence or absence of a heart failure hospitalisation event and the presence or absence of a history of heart failure hospitalisation events. The model also includes two death states; cardiovascular death and background mortality.
Cycle length	4 months.
Patient characteristics and circumstances of use	<p>Mean age, proportion male and baseline distribution across CKD stages was estimated based on the FIDELITY <i>post hoc</i> subgroup of patients with UACR <math>\geq</math> 200 mg/g (6.6% with SGLT2i use).</p> <p>The model assumed that patients had no prior history of heart failure hospitalisation.</p> <p>Finerenone adherence and persistence estimates were based on the FIDELITY whole study population. The use of background therapies was estimated based on the baseline use of medications from the FIDELITY whole study population, adjusted for increased use of SGLT2i medicines (based on the DAPA-CKD trial).</p>
Transition probabilities	<p>Placebo CKD health state transitions, heart failure hospitalisation risks and the risk of cardiovascular death were based on individual patient data from the FIDELITY pooled analysis subgroup of patients with baseline UACR <math>\geq</math> 200 mg/g without SGLT2i use, adjusted for SGLT2 inhibitor treatment effects (from the DAPA-CKD trial type 2 diabetes subgroup) in the proportion of patients not intolerant to treatment (based on the DAPA-CKD trial). Transitions between the dialysis and transplant states were based on the transplant rate in Australian dialysis patients (ANZDATA 2020).</p> <p>The risks of hyperkalaemia events were based on individual patient data from the FIDELITY pooled analysis subgroup of patients with baseline UACR <math>\geq</math> 200 mg/g without SGLT2i use, with</p>

Component	Description
	<p>no adjustment for SGLT2i treatment effects.</p> <p>The risk of background mortality was based on Australian life tables adjusted to exclude cardiovascular causes of death with additional mortality multipliers applied from the published literature.</p> <p>Finerenone treatment effects were estimated based on pre-specified and <i>post hoc</i> analyses of the FIDELITY FAS pooled data with additional assumptions. Treatment effects were assumed to remain constant over time while on treatment. The risk of treatment discontinuation was also based on the pooled FIDELITY analysis assuming that the rate of discontinuation remains constant over time. Patients discontinuing finerenone treatment were assumed to have the same risk as placebo patients.</p>
Utility values	Utility/disutility values were unchanged in the resubmission; derived from a <i>post hoc</i> analysis of EQ-5D-5L utility data from the pooled FIDELITY analysis.
Costs	<p>Finerenone drugs costs were estimated based on the proposed price and adherence based on the pooled FIDELITY analysis.</p> <p>Background therapy costs were estimated based on the utilisation of different drug classes in the pooled FIDELITY analysis with costs estimated for a representative member of each drug class using published PBS prices. The proportion of patients using an SGLT2i was updated to account for the revised proposed restriction requiring finerenone treatment in combination with an SGLT2i unless medically contraindicated or intolerant. The proportion of patients intolerant or contraindicated to SGLT2i medicines was based on the incidence of adverse events leading to dapagliflozin discontinuation in the DAPA-CKD trial (Heerspink 2020).</p> <p>The cost of hyperkalaemia without hospitalisation was based MBS costs assuming that patients would require a specialist visit and a serum potassium test. The cost of hyperkalaemia with hospitalisation was based on AR-DRG cost weights.</p> <p>The cost of acute heart failure was based on AR-DRG cost weights. The resubmission assumed no chronic costs for heart failure patients.</p> <p>The costs of CKD health states (CKD 1/2,3,4,5) were based on published estimates for diabetic kidney disease from an Australian costing study (Wyld 2015). The costs of acute/chronic dialysis were estimated based on previously published data from NSW Health (NSW Dialysis Costing Studies, 2009). The costs of transplantation were updated from a modelled economic analysis of diabetes, hypertension, and chronic kidney disease management in Australia (Howard 2010) and a published comparative modelled analysis of dialysis and transplantation in Australia (Wong 2012).</p> <p>The cost of cardiovascular death was assumed to be the same as a non-fatal heart failure event. The resubmission assumed no costs associated with background mortality.</p> <p>Costs estimated in the resubmission were inflated to 2020 values using the AIHW Total Health Price Index.</p>

Source: Table 68, p112-114 of the resubmission.

Abbreviations: CKD, chronic kidney disease; FAS, full analysis set; SGLT2i, sodium-glucose co-transporter-2 inhibitor; UACR, urinary albumin-to-creatinine ratio.

- 6.40 All patients began the model with various levels of renal impairment (CKD 1/2, CKD 3, CKD 4) with the assumption of no prior history of heart failure hospitalisation. During each cycle of the Markov model, patients could remain in their current health state, experience progression/regression of renal impairment, initiate dialysis or transplantation, experience a non-fatal heart failure hospitalisation event, or die from cardiovascular or background mortality. Patients experiencing a non-fatal heart failure hospitalisation or initiating dialysis/transplantation transition to a corresponding

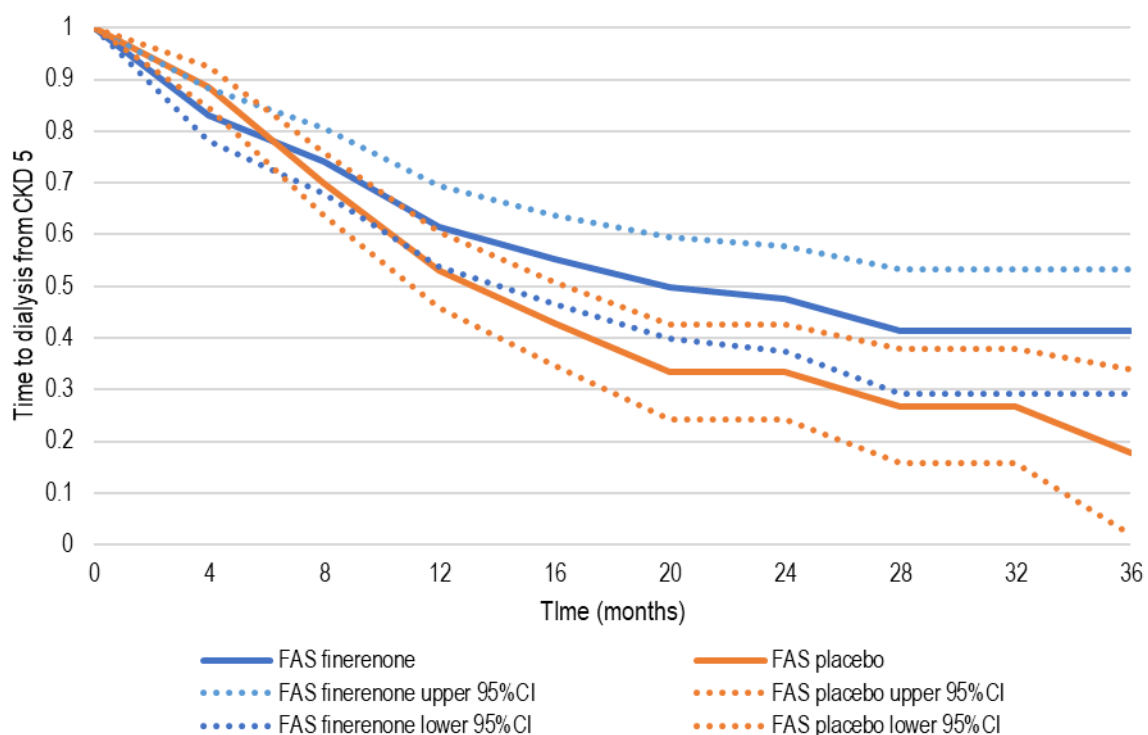
chronic disease state in the next cycle. Patients in both treatment arms could also experience hyperkalaemia events with or without hospitalisation in any cycle. Patients in the finerenone arm could discontinue treatment in any cycle and adopt the same risks as the placebo arm.

- 6.41 Baseline patient characteristics used in the model, based on the FIDELITY *post hoc* UACR  $\geq 200$  mg/g subgroup, are unlikely to reflect the proposed PBS population given only 6.6% of patients in the subgroup were using SGLT2i medicines, and it is highly likely that broader SGLT2i use will select a population with a different distribution between CKD stages to the modelled population. The PSCR argued that based on an analysis of the OneNil dataset and the consideration that the target population are using an SGLT2i (unless medically contraindicated or intolerant) the proposed PBS population will likely have more severe renal disease compared to the patient population modelled in the economic evaluation. Given that the cost-effectiveness of finerenone improves for patients with more severe baseline renal disease, the PSCR considered that the baseline distribution across CKD stages in the economic model is conservative (see Table 15). The ESC noted the evaluation had concluded analyses of the OneNil database were poorly supported and unlikely to be representative of the target PBS population. Although it is likely that patients using an SGLT2 inhibitor would have more severe renal disease, any treatment effect of SGLT2 inhibitors (prior to the modelled baseline) is not accounted for.
- 6.42 In response to PBAC concerns that the model structure did not appropriately account for the relationship between renal disease progression, risk of hyperkalaemia and treatment discontinuation (para 7.10, Finerenone PSD, July 2022 PBAC meeting), the resubmission revised the risks of hyperkalaemia to vary by CKD stage and introduced treatment discontinuation due to hyperkalaemia. The resubmission also estimated risks of subsequent heart failure hospitalisation by CKD stage (the July 2022 submission assumed a constant risk of subsequent cardiovascular events independent of CKD stage). Risks of overall treatment discontinuation are unchanged, however, and are assumed to be independent of CKD stage. This is inconsistent with the clinical data which suggest higher discontinuation rates in patients with more severe renal impairment. The PSCR argued that rates of treatment discontinuation increase with CKD stage, based on the increasing risk of hyperkalaemia related discontinuation (4-monthly probability of treatment discontinuation CKD1/2 = 0.09%; CKD3 = 0.39%; CKD4 = 0.69%; CKD5/no RRT = 1.24%). The ESC considered that the inclusion of hyperkalaemia-related discontinuation based on CKD stage only partly addresses the previous matter of concern and considered that the assumption of a constant risk of finerenone treatment discontinuation independent of CKD stage does not account for the relationship between renal disease progression and treatment discontinuation. The pre-PBAC response provided a revised economic model in response to the ESC advice above by increasing probabilities of background risk of discontinuation by an additional non-specific 10% in each CKD stage (submission base case: CKD1/2 = 3.48%,

CKD3 = 3.78%, CKD4 = 4.08%; pre-PBAC response: CKD5 = 4.63%; CKD1/2 = 3.48%, CKD3 = 4.12%, CKD4 = 4.76%, and CKD5 = 5.64%).

6.43 At the July 2022 meeting, the PBAC considered that it was inappropriate for the submission to have assumed independent finerenone treatment effects for progression to CKD stage 5 and progression to dialysis, given that both treatment effects share a high degree of overlap (para 7.10, Finerenone PSD, July 2022 PBAC meeting). To address PBAC’s concern, the resubmission presented the results of a *post hoc* analysis of time to dialysis after a patient had reached CKD stage 5 (eGFR < 15 mL/min/1.73 m<sup>2</sup>). The results based on the overall FIDELITY pooled population are summarised in Figure 1 below. The resubmission also presented results based on the UACR ≥ 200 mg/g subgroup, with results for the UACR ≥ 200 mg/g with SGLT2i use and UACR ≥ 200 mg/g without SGLT2i use subgroups provided in Attachment 11 to the resubmission.

Figure 1: Time to dialysis in patients who progress to CKD 5



Number of subjects										
FIN	280	152	104	64	46	26	23	13	13	13
PBO	317	202	124	70	40	16	16	8	8	2
Cumulative number with dialysis event										
FIN	0	36	50	65	71	74	75	77	77	77
PBO	0	29	67	93	104	110	110	112	112	113

Source: Figure 30, p172 of the resubmission and New episode of dialysis spreadsheet, Attachment 11 of the resubmission. Abbreviations: CI, confidence interval; CKD, chronic kidney disease; FAS, full analysis set; FIN, finerenone; PBO, placebo.

6.44 The analysis indicated that after an initial increase in progression to dialysis compared with placebo, finerenone treatment was associated with a delay in progression to

dialysis compared with placebo beyond 8 months, although confidence intervals are overlapping.

- 6.45 Limited details were presented on the analysis and the data could not be validated during the evaluation. The number of placebo arm patients proceeding to dialysis from CKD stage 5 (N=113), was higher than the number based on FIDELITY individual patient data presented in the July 2022 submission (N=82). It was unclear whether the number of patients at each time point represented patients actively receiving treatment or whether they were based on randomised treatment regardless of active treatment status. Additionally, there is substantial loss of data within a very short period of this analyses with no documentation of reasons for censoring and unclear outcomes of missing patients.
- 6.46 The results presented in the resubmission were suggestive of a treatment effect for finerenone on progression to dialysis from CKD stage 5, however, the magnitude of any treatment benefit is unclear. The economic model assumes fully independent treatment effects for progression from CKD stages 1-4 to stage 5 (eGFR < 15 mL/min/1.73 m<sup>2</sup>) and CKD stages 1-5 to dialysis, with the treatment effect estimates not accounting for overlap between the estimates. The treatment effect applied to transitions from CKD stage 1-4 to CKD stage 5 without dialysis/transplantation included patients with and without progression to dialysis/transplant. The treatment effect applied to transitions from CKD stage 1-4 to dialysis and CKD stage 5 to dialysis included patients with and without a sustained decrease in eGFR to < 15 mL/min/1.73 m<sup>2</sup>. The magnitude of treatment effect accounting for the overlap in outcomes for each of these transitions is unclear. The PSCR (2-3) acknowledged that the data informing the transitions from CKD stage 1-4 to CKD stage 5 and from CKD stage 1-5 to dialysis were based on overlapping populations, however it argued that the impact of any overlap was likely to be small. The ESC considered that that the assumption of independent treatment effect estimates, not adjusted for overlap, applied to transitions from CKD stage 1-4 to CKD stage 5 and from CKD stage 1-5 to dialysis in the base case analysis is not appropriate as it overestimates the magnitude of effect for finerenone.
- 6.47 Although no changes have been made to finerenone treatment effects on renal outcomes in the resubmission, the model has been revised to allow separate finerenone treatment effects to be applied to transitions from CKD stage 1-4 to dialysis and from CKD stage 5 to dialysis, so that any uncertainty regarding overlapping treatment effects can be explored.
- 6.48 The resubmission stated that clinician input was sought to address ESC concerns that once CKD stage 5 is reached, the decision to commence dialysis is often a patient decision or related to access and is unlikely to be influenced by finerenone use in practice (Table 13, Finerenone PSD, July 2022 PBAC meeting). The resubmission stated that the feedback was based on two specialist workshops conducted in October 2022 including nephrologists and endocrinologists from Melbourne and Sydney. The advice was that progression to dialysis could be affected by treatment and that the treatment

effect observed in CKD 5 patients in the trial was plausible. No further information was provided on the expert opinion, and it was unclear what data were presented to the specialists.

6.49 The pre-PBAC response provided a revised economic model in response to the ESC advice above with equal rates of progression from CKD 5 to dialysis in both arms of the model (hazard ratio [HR] = 1).

6.50 Key drivers of the economic model are summarised in Table 12.

**Table 12: Key drivers of the model**

Description	Method/Value	Impact
Baseline patient characteristics	<p>Baseline patient characteristics in the economic model (age, proportion male, distribution between CKD stages) were based on FIDELITY UACR <math>\geq</math> 200 mg/g subgroup.</p> <p>The use of the FIDELITY UACR <math>\geq</math> 200 mg/g subgroup as the source of baseline characteristics (with only 6.6% of patients using SGLT2i medicines) assumed that the use of SGLT2i medicines would not affect the baseline characteristics of patients (i.e. baseline distribution of CKD health states) which was inconsistent with the available data from the target subgroup and inconsistent with the modelled treatment effects for SGLT2i medicines applied in the model. Overall, it is highly likely that SGLT2i use will select a population with different characteristics to the modelled population.</p> <p>Additionally, the impact of quota sampling in the FIDELIO-DKD and FIGARO-DKD trials, which limited the proportion of the trial population with certain patient characteristics (e.g. eGFR <math>\geq</math> 60 to <math>&lt;</math> 75 mL/min/1.73 m<sup>2</sup> and very high albuminuria), on the post hoc subgroups with UACR <math>\geq</math> 200 mg/g is unclear.</p>	High, favours finerenone
Subsequent heart failure hospitalisation	<p>Risks of subsequent heart failure hospitalisation were derived by adjusting transition probabilities in patients in the FIDELITY UACR <math>\geq</math> 200 mg/g SGLT2i non-user subgroup by SGLT2i treatment effects in the proportion of patients using SGLT2i medicines.</p> <p>A calculation error (which did not adequately account for the numbers of patients at risk) resulted in a significant overestimation of subsequent heart failure hospitalisation events in the FIDELITY UACR <math>\geq</math> 200 mg/g SGLT2i non-user subgroup (4-monthly risks 19.4% to 43.9%). The PSCR acknowledged an error was made in the economic evaluation and accepted the results of the revised base case.</p> <p>Based on FIDELITY individual patient data, 103 subsequent heart failure hospitalisations occurred in the 4,547 placebo arm patients in the UACR <math>\geq</math> 200 mg/g SGLT2i non-user subgroup over 56 months. The model (with SGLT2i treatment effects removed) estimated that 775 heart failure hospitalisations would occur over the same time period in a cohort of 4,547 patients. Using alternative risks calculated during the evaluation (4-monthly risks 1.48% to 13.8%) resulted in 119 events in the cohort of 4,547 patients based on the FIDELITY UACR <math>\geq</math> 200 mg/g SGLT2i non-user subgroup over 56 months, more consistent with the FIDELITY individual patient data.</p>	High, favours finerenone
Finerenone treatment effects	The PBAC previously considered that it was inappropriate for the July 2022 submission to have assumed independent finerenone treatment effects for progression to CKD stage 5 and progression to dialysis, given that both	High, favours finerenone

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Description	Method/Value	Impact
	<p>treatment effects share a high degree of overlap (para 7.10, Finerenone PSD, July 2022 PBAC meeting).</p> <p>The resubmission argued that separate treatment effects were supported by the clinical data (see Figure 1 above) and no changes have been made to finerenone treatment effects on renal outcomes in the resubmission.</p> <p>The data presented in the resubmission were suggestive of a treatment effect for finerenone on progression to dialysis from CKD stage 5. However, the treatment effect estimates applied to transitions from CKD stage 1-4 to CKD stage 5 and from CKD stage 1-5 to dialysis have not been adjusted to account for the overlap between estimates. Accounting for the overlap in outcomes for each of these transitions is likely to result in a smaller magnitude of effect for finerenone. The assumption was revised in the pre-PBAC response (see paragraph 6.49)</p>	
Finerenone treatment discontinuation	<p>The economic analysis used a constant risk of finerenone treatment discontinuation (3.4% per 4-month cycle), based on data from the finerenone arm of the FIDELITY pooled analysis. This was unchanged from the July 2022 submission.</p> <p>The PBAC previously considered that varying finerenone treatment discontinuation by CKD stage would reflect clinical practice, whereby treatment discontinuation becomes more likely as renal function impairment progresses (para 7.10, Finerenone PSD, July 2022 PBAC meeting). The impact of varying finerenone treatment discontinuation by CKD stage was not able to be assessed during the evaluation. The discontinuation rate was revised in the pre-PBAC response (see paragraph 6.42)</p>	Unclear impact

Source: Constructed during the evaluation.

Abbreviations: SGLT2i, sodium-glucose co-transporter-2 inhibitor; UACR, urinary albumin-to-creatinine ratio.

- 6.51 The ESC considered the health state utility values used in the July 2022 model were high compared to other values reported in the literature, considered the relativities between the trial-based utilities to be implausible in some cases, and advised they be replaced by values obtained from the literature (para 6.38, Finerenone PSD, July 2022 PBAC meeting). The utilities used in the base case economic evaluation are unchanged from the July 2022 submission. However, estimates from a systematic review of health utility values across different CKD stages and renal replacement therapies (Cooper 2020) were used in a sensitivity analysis. The utility/disutility estimates had a minimal impact on the economic analysis.
- 6.52 At the July 2022 meeting, the PBAC considered that the submission’s base case (\$5,000 to < \$15,000 per QALY gained) was optimistic and the alternative base case conducted during the evaluation (removing dialysis access surgery costs, using the AIHW total health price index to inflate dialysis cost estimates, and removing the finerenone treatment effect on progression to dialysis), with an ICER of \$55,000 to < \$75,000 per QALY gained, remained uncertain and was a likely underestimate. The PBAC considered that finerenone as an add-on to standard of care including an SGLT2i, was unlikely to be cost-effective at a price greater than that accepted for dapagliflozin for CKD (para 7.9, Finerenone PSD, July 2022 PBAC meeting).

- 6.53 The PBAC considered the model's structure and inputs were optimistic, citing the following issues (para 7.10, Finerenone PSD, July 2022 PBAC meeting):
- the pooled FIDELITY analysis did not reflect the proposed PBS population with very high albuminuria and expected use of SGLT2i medicines.
  - the submission assumed independent treatment effects for progression to CKD stage 5 and progression to dialysis.
  - the finerenone treatment effect on the composite cardiovascular outcome was not supported.
  - the model did not appropriately account for the relationship between renal disease progression, risk of hyperkalaemia and treatment discontinuation.
  - the costs of dialysis were overestimated.
- 6.54 The resubmission argued that the model had been revised in line with PBAC advice, the revised ICER (\$5,000 to < \$15,000 per QALY gained) can be considered cost-effective and the proposed listing of finerenone in a targeted CKD population provides reasonable justification for a higher price than for dapagliflozin for CKD.
- 6.55 The ESC considered that although the resubmission addressed a number of the issues identified by the PBAC, the resubmission's model significantly overestimated subsequent heart failure hospitalisation, and a number of uncertainties were not addressed in the resubmission, including:
- uncertainty regarding baseline patient characteristics (based on the FIDELITY UACR  $\geq 200$  mg/g SGLT2i non-user subgroup, adjusted for SGLT2i treatment effects [DAPA-CKD trial diabetes subgroup]);
  - the assumed independent treatment effects for progression to CKD stage 5 and progression to dialysis unadjusted for overlap;
  - uncertainty of magnitude of treatment benefit of finerenone for patients receiving an SGLT2i (based on the FIDELITY whole study (FAS) population); and
  - the overall finerenone treatment discontinuation was assumed to be independent of CKD stage.
- 6.56 During the evaluation, a revised base case was calculated correcting for the overestimation of subsequent heart failure hospitalisation events and correcting an error that applied finerenone treatment effects on subsequent heart failure hospitalisation to patients who had discontinued treatment. The results of the revised analysis as presented in the resubmission are summarised in Table 13. The PSCR acknowledged an error was made in the economic evaluation and accepted the results of the revised base case.

**Table 13: Results of the economic evaluation as presented in the resubmission**

	Finerenone	Placebo	Increment
Costs (\$)		\$97,405	
QALYs	6.4317	6.3723	0.0594
Incremental cost per QALY gained			<sup>1</sup>

Source: Constructed during the evaluation using the 'Section\_3\_model.xlsx' spreadsheet provided with the resubmission.

Abbreviation: QALY, quality adjusted life year.

Note: The analysis uses alternative subsequent heart failure hospitalisation risks calculated during the evaluation and corrects an error in the model spreadsheet which applied finerenone treatment effects on subsequent heart failure hospitalisations to patients who had discontinued treatment (column CC of the 'FIN Trace' spreadsheet of the 'Section\_3\_model.xlsx' economic model).

The redacted values correspond to the following ranges:

<sup>1</sup> \$25,000 to < \$35,000

- 6.57 Based on the revised base case of the resubmission, treatment with finerenone was associated with an incremental cost per QALY gained of \$25,000 to < \$35,000 compared to placebo for the management of diabetic kidney disease in patients with high/very high albuminuria and SGLT2 inhibitor use, unless contraindicated or intolerant. This compares with the base case estimate presented in the resubmission of \$5,000 to < \$15,000 per QALY gained.
- 6.58 In the model, 92% of incremental QALYs; 51% of finerenone drug costs; 89% of incremental disease management costs (background medication, health state and adverse event costs); and 88% of cost offsets (due to decreased costs for dialysis, transplantation, and cardiovascular events) were accrued in the extrapolated period beyond 3 years.
- 6.59 For every 1,000 patients treated with finerenone versus placebo and followed up for 15 years, the economic evaluation revised during the evaluation (without discounting) estimated that there would be:
- Additional finerenone drug costs of \$|| with additional disease management costs of \$|| (background medications, health state costs and adverse events).
  - Decreased incidence of dialysis (14 fewer initiations), transplant (4 fewer transplants), heart failure hospitalisation (44 fewer events), fatal cardiovascular events (8 fewer deaths) and other deaths (4 fewer deaths).
  - Increased incidence of hyperkalaemia without hospitalisation (224 events) and hyperkalaemia with hospitalisation (22 events).
  - Decreased costs for dialysis (\$||), transplantation (\$||), and cardiovascular events (\$||).
- 6.60 As noted above, the pre-PBAC response provided a revised economic model with amendments to the HR applied to patients transitioning from CKD 5 to dialysis (HR = 0.819 to HR = 1) and the 4-monthly probabilities for treatment discontinuation by CKD stage (submission base case : CKD1/2 = 3.48%, CKD3 = 3.78%, CKD4 = 4.08%; pre-PBAC response: CKD5 = 4.63%; pre-PBAC response: CKD1/2 = 3.48%, CKD3 = 4.12%, CKD4 = 4.76%, and CKD5 = 5.64%). The pre-PBAC response also proposed a price reduction for finerenone from \$| AEMP to \$| AEMP. The resulting cost-effectiveness results are provided in Table 14. It is noted that the revised economic model also corrected the error identified during evaluation (see paragraph 6.56).

**Table 14: Results of the updated economic evaluation provided in the pre-PBAC response**

	Finerenone	Placebo	Increment
Costs (\$)		\$100,988	
QALYs	6.414	6.365	0.049
Incremental cost per QALY gained			<sup>1</sup>

Source: 'Item 7.07 Pre PBAC Response finerenone (Kerendia) Section\_3\_model\_new base case\_revised.xlsx', provided in the pre-PBAC response

Abbreviation: QALY, quality adjusted life year

The redacted values correspond to the following ranges:

<sup>1</sup> \$5,000 to < \$15,000

6.61 The results of sensitivity analyses conducted using the resubmission's base case are presented in Table 108, pp180-182 of the resubmission. Key sensitivity analyses conducted during the evaluation based on the revised base case are summarised in Table 15.

**Table 15: Results of sensitivity analyses (conducted using the resubmission's base case)**

Analyses	Incremental cost (\$)	Incremental QALYs	ICER	% change from base case
<b>Base case</b>		<b>0.0594</b>	<b>1</b>	<b>-</b>
- 0% costs and outcomes		0.0915	2	-40%
- 3.5% costs and outcomes		0.0673	1	-13%
- 5 years		0.0123	3	+538%
- 10 years		0.0368	4	+81%
- 30 years		0.0826	2	-24%
All patients in CKD 1/2 at baseline		0.0448	4	+124%
All patients in CKD 3 at baseline		0.0666	2	-28%
All patients in CKD 4 at baseline		0.1012	Dominant	NE
Patient characteristics based on FIDELITY whole study population (age 65; 69.8% male; 39.9% CKD 1/2; 53.3% CKD 3, 6.8% CKD 4)		0.0603	1	+6%
Patient characteristics based on FIDELITY UACR ≥ 200 mg/g SGLT2i user subgroup (age 60; 74.7% male; 63.0% CKD 1/2; 35.8% CKD 3, 1.2% CKD 4)		0.0529	5	+30%
Patient characteristics based on OneNil analysis (age 65; 58.2% male; 36.2% CKD 1/2; 47.7% CKD 3; 16.1% CKD 4)		0.0643	2	-30%
Decrease mean age to 60 years		0.0589	2	-22%
Increase mean age to 70 years		0.0573	6	+55%
CKD health state transition probabilities based on FIDELITY whole study population		0.0649	2	-20%
CKD health state transition probabilities based on FIDELITY UACR ≥ 200 mg/g subgroup		0.0634	7	-70%
CKD health state transition probabilities based on FIDELITY UACR ≥ 200 mg/g SGLT2i user subgroup		0.0599	6	+68%
Treatment effects based on FIDELITY UACR ≥ 200 mg/g subgroup		0.0611	1	-10%
Treatment effects based on FIDELITY UACR ≥ 200 mg/g SGLT2i user subgroup		0.2257	8	-96%
Remove progression to CKD stage 5 treatment effect		0.0456	4	+141%
Remove dialysis treatment effect		0.0542	4	+89%

Analyses	Incremental cost (\$)	Incremental QALYs	ICER	% change from base case
Remove dialysis treatment effect for patients in CKD stage 5		0.0579	5	+29%
Remove dialysis treatment effect for patients in CKD stages 1-4		0.0557	6	+58%
Finerenone 100% adherence		0.0594	5	+25%
Finerenone price based on dapagliflozin CKD DPMQ (\$56.97)		0.0594	Dominant	NE
Increase dialysis costs by 25%		0.0594	2	-46%
Decrease dialysis costs by 25%		0.0594	5	+46%

Source: Constructed during the evaluation using the 'Section\_3\_model' spreadsheet provided with the resubmission.

Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; FAS, full analysis set; HHF, hospitalisation for heart failure; ICER, incremental cost effectiveness ratio; NE, not estimable; QALY, quality adjusted life year; SGLT2i, sodium-glucose co-transporter-2 inhibitor; UACR, urinary albumin-to-creatinine ratio.

The redacted values correspond to the following ranges:

- <sup>1</sup> \$25,000 to < \$35,000
- <sup>2</sup> \$15,000 to < \$25,000
- <sup>3</sup> \$155,000 to < \$255,000
- <sup>4</sup> \$55,000 to < \$75,000
- <sup>5</sup> \$35,000 to < \$45,000
- <sup>6</sup> \$45,000 to < \$55,000
- <sup>7</sup> \$5,000 to < \$15,000
- <sup>8</sup> \$0 to < \$5,000

6.62 The results of the sensitivity analyses indicated that the model was most sensitive to a shorter time horizon, population characteristics informing baseline risk (age, CKD stage distribution), placebo arm transition probabilities between CKD stage/kidney failure health states, finerenone treatment effects (particularly for renal outcomes), and dialysis costs. The impact of varying finerenone treatment discontinuation by CKD stage was not able to be assessed during the evaluation.

### Drug cost/patient/year

6.63 The resubmission proposed a flat pricing structure for both dose strengths (10 and 20 mg) of finerenone. The estimated drug cost for finerenone per patient per year was \$| (based on the proposed DPMQ per script of \$| / 28 days per script × 365 days per year). This was unchanged from the July 2022 submission. Incorporating 91.74% adherence from the pooled FIDELITY analysis, the estimated drug cost for finerenone per patient per year was \$| (\$| × 91.74%). As stated previously, the pre-PBAC response proposed a price reduction for finerenone from \$| AEMP (\$| DPMQ) to \$| AEMP (\$| DPMQ). The estimated cost for finerenone per patient per year based on this price reduction is \$| (based on the proposed DPMQ per script of \$| / 28 days per script × 365 days per year). Incorporating 91.74% adherence from the pooled FIDELITY analysis, the estimated drug cost for finerenone per patient year is \$| (\$| × 91.74%).

6.64 A comparison of finerenone use between the trial setting, economic model and budget impact model is presented in Table 16.

**Table 16: Calculation of drug cost per year**

	FIDELITY pooled analysis	Economic model	Financial estimates
Finerenone script cost (DPMQ)	-	\$(resubmission) \$█ (pre-PBAC response)	\$(resubmission) \$█ (pre-PBAC response)
Treatment adherence	91.7%	91.7%	91.7%
Treatment persistence	66.1% at 4 years	54.8% at 4 years <sup>a</sup>	Not directly estimated, finerenone was assumed to modify uptake rates in the prevalent population

Source: Table 86, p151; Table 91, p159; Section 4.2.1, p192 of the resubmission; Section\_3\_model provided with the resubmission

<sup>a</sup> Based on the proportion of patients in the on finerenone health states in cycle 12 of the economic model (without half-cycle correction); includes treatment discontinuation based on the FIDELITY estimate of persistence of 66.1% at 4 years (3.4% per cycle); with additional discontinuation due to hyperkalaemia, and death.

### **Estimated PBS usage & financial implications**

- 6.65 This submission was not considered by DUSC. The resubmission used an epidemiological approach to estimate the utilisation and financial impact of listing finerenone on the PBS/RPBS.
- 6.66 The target population used in the estimates was narrowed to be consistent with the population proposed by the PBAC at the July 2022 meeting (para 7.3, Finerenone PSD, July 2022 PBAC meeting); i.e. patients with more severe diabetic kidney disease (baseline UACR  $\geq 200$  mg/g was proposed in the resubmission rather than UACR  $\geq 300$  mg/g), excluding patients with HFREF, and as an add-on to standard of care comprising an ACEi or ARB and SGLT2i unless contraindicated. The resubmission acknowledged the concerns of the PBAC and the ESC about the applicability of the OneNil dataset to the proposed Australian population, but preferred the OneNil estimate of the proposed population (UACR  $\geq 200$  mg/g and eGFR  $\geq 25$  mL/min/1.73 m<sup>2</sup>; SGLT2i use and intolerance), as it was considered to be more precise relative to estimates presented in the dapagliflozin PSD (CKD).
- 6.67 In addition, the estimated use and financial implications excluded patients with eGFR  $\leq 25$  mL/min/1.73 m<sup>2</sup>, known significant non-diabetic renal disease, treatment with another selective nonsteroidal mineralocorticoid-receptor antagonist or a renin inhibitor or with a serum potassium  $> 4.8$  mmol/L, consistent with the requested restriction.
- 6.68 The resubmission followed the approach proposed by the PBAC at the July 2022 meeting, using the prevalent T2D population as the basis for determining the proposed prevalent population, from which the proportion of patients meeting the UACR, eGFR, ACE/ARB and serum potassium criteria was determined, and SGLT2i medicine use and uptake determined discretely.
- 6.69 Key inputs relied on in the financial estimates are summarised in Table 17.

**Table 17: Key inputs for financial estimates**

Data	Value and source	Comment
<b>Eligible population and treatment utilisation</b>		
Australian prevalence of T2D	Based on the ABS population forward estimates (3222.0 Series B, 2023-2028), and	The evaluation considered this was broadly consistent with the approach proposed by the PBAC

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Data	Value and source	Comment
	the estimated prevalence of T2D by age and sex in the AIHW Diabetes Web report 2020 (NDSS/APEG linked data).	<p>at the July 2022 meeting. However, the ESC noted that the PBAC proposed an approach that estimated the number of patients with diabetes according to the number of individuals receiving medicines for diabetes in Australia (para 7.11, Finerenone PSD, July 2022 PBAC meeting) and considered that a mixed market share/epidemiological approach may have been more appropriate to estimate the eligible population for finerenone.</p> <p>The resubmission inappropriately included a small number of children aged 0-17 years in the estimated Australian prevalence of T2D.</p> <p>The AIHW estimates were based on NDSS/APEG and ABS National Health Survey data acknowledged to have most likely underestimated the prevalence of T2D, given both sources reported voluntary patient registrations of diagnosed diabetes (50% of T2D may be undiagnosed; AusDiab Study 2019-2000).</p>
Proportion of T2D patients with UACR $\geq$ 200 mg/g and eGFR $\geq$ 25 mL/min/1.73 m <sup>2</sup>	<p>12.1%: Based on a commissioned analysis of the OneNil dataset. T2D in the OneNil analysis was based on coded diagnoses in clinical files at any time in history, or a recent HbA1c <math>\geq</math> 6.5%.</p> <p>UACR and eGFR criteria were met, if satisfied at any time during a diagnosis with T2D.</p> <p>Patients with UACR 'AND' eGFR were only included if both criteria were met in the same calendar year.</p>	<p>The OneNil analysis did not differentiate between transient (e.g. infection related) or persistent albuminuria (i.e. abnormalities of kidney structure or function present for 3 months or more), and included patients with non-diabetic kidney disease, HFrEF with an indication for an MRA or treatment with a potassium-sparing diuretic. Of 3,983 patients with UACR/eGFR records, 600 had UACR <math>\geq</math> 200 mg/g, and 480 also had an eGFR between 30-90 mL/min/1.73 m<sup>2</sup>. Given the analysis may have included patients otherwise excluded in the requested restriction, and did not include patients with eGFR <math>\geq</math> 90 mL/min/1.73 m<sup>2</sup> (&lt; 10 patients in the study), the estimated proportion may not be applicable to the proposed Australian population and is highly uncertain.</p> <p>The ESC noted that the AusDiab data (Atkins et al 2004) suggested previously by the PBAC reported 4.6% of participants had macroalbuminuria. It was noted the submission stated estimates from the AusDiab study regarding prevalence of patient meeting UACR <math>\geq</math> 200 mg/g could not be obtained from the literature.</p>
Proportion of high-risk DKD patients on an ACEi or ARB	76%: Based on the estimate proposed by the PBAC at the July 2022 meeting (para 7.11, finerenone PSD, July 2022 PBAC meeting), derived from the CKD-FIX study, a study of 369 patients admitted to 31 Australian and New Zealand hospitals, with CKD stage 3 or 4, at increased risk of disease progression (Badve et al. 2020).	Badve et al. 2020 noted that 76% of patients in the study were taking a RAASi medicine at baseline. Patients with HFrEF were not excluded. Given all patients in the study were hospitalised, and the majority had non-diabetic kidney disease (55%) versus DKD (45%), the observations of Badve et al. (2020) may not be applicable to the proposed Australian population.
Proportion of patients currently on SGLT2i (or intolerant/contraindicated)	24.1%: calculated from 18.6% SGLT2i use and 5.5% SGLT2i intolerance. The estimated use of SGLT2i medicines was based on 18 of 97 patients in the OneNil analysis aged > 18 years, with ACEi/ARB use, not on an MRA,	Given the small number of potentially eligible patients in the selected OneNil dataset and the inclusion of patients otherwise excluded in the requested restriction (see above), the estimated SGLT2i medicine use based on 18/97 patients is

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Data	Value and source	Comment
	with UACR $\geq$ 200 mg/g and eGFR $\geq$ 25 mL/min/1.73 m <sup>2</sup> , and serum K <sup>+</sup> $\leq$ 5 mmol/L. SGLT2i intolerance was derived from the dapagliflozin discontinuation rate due to adverse events in the DAPA-CKD trial (Table 8, dapagliflozin PSD, November 2021 PBAC meeting).	highly uncertain. The proportion of patients intolerant to or contraindicated SGLT2i medicines was most likely underestimated, as the DAPA-CKD most likely excluded patients contraindicated SGLT2i medicines.
Expected uptake of SGLT2i medicines in the untreated population	65-85%: Inferred from estimates presented in Table 18 of the dapagliflozin (CKD) PSD (November 2021 PBAC meeting). The resubmission calculated the estimated uptake using numbers of patients not treated with SGLT2i but eligible for the CKD listing, and total patients treated (footnoted ranges used for redacted totals).	Uptake rates in the dapagliflozin submission were assumed, and considered underestimates by the DUSC (para 7.9, dapagliflozin PSD, November 2021 PBAC meeting). SGLT2i uptake rates were increased, as noted in the addendums to the dapagliflozin submission, but were not used in the resubmission. The ESC agreed with the evaluation that the uptake of SGLT2i medicines in the eligible Australian population may be underestimated. It was noted the economic model assumes 94.5% of patients will be on an SGLT2 inhibitor.
Proportion of patients with persistent UACR $\geq$ 200 mg/g despite treatment with SGLT2i	69.1%: Derived from the DAPA-CKD trial (para 7.11, finerenone PSD, July 2022 PBAC meeting). This value was only applied to potentially eligible patients expected to uptake SGLT2i in the untreated population.	At the July 2022 meeting, the PBAC cited the percentage of patients with persistent UACR $>$ 300 mg/g as 64% in the DAPA-CKD trial (para, 7.11, finerenone PSD, July 2022 PBAC meeting). The basis of the inflated estimate, which may be to account for the broader UACR range, is unclear. The ESC considered this percentage should apply to the entire patient population as the proposed continuing restriction includes UACR criteria.
Uptake of finerenone in the eligible population	█-█%: Uptake rates in the July 2022 submission were calculated to account for increased uptake over time and discontinuation due to death or initiation of RRT. The resubmission stated the uptake rates are higher than the previous submission, consistent with targeted population, but lower than the estimated uptake of SGLT2i medicines in the untreated DKD population.	At the July 2022 meeting the ESC noted that finerenone uptake rates were implausibly high given the evolving treatment landscape and the discontinuation rates in the pivotal trials (34% at 4 years in FIDELITY), and should be substantially lower (Table 18, finerenone PSD, July 2022 PBAC meeting). The uptake of finerenone in the narrower population proposed in the resubmission is uncertain. The ESC considered the uptake assumed in the resubmission was likely to be an overestimate.
Adherence	91.7%: Based on the mean adherence reported in the FIDELITY resubmission pooled analysis.	Adherence observed in the clinical trials is unlikely to be realised in clinical practice, and may be overestimated.

Source: Sections 4.1.1 and 4.1.2, pp184-194 of

Abbreviations: ABS, Australian Bureau of Statistics; ACEi, angiotensin converting enzyme inhibitor; AIHW, Australian Institute of Health and Welfare; APEG, Australasian Paediatric Endocrine Group; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; NDSS, National Diabetes Services Scheme; PBS, Pharmaceutical Benefits Scheme; PSD, public summary document; RAASi, renin angiotensin aldosterone system inhibitor; RRT, renal replacement therapy; SGLT2i, sodium glucose co-transporter 2 inhibitor; T2D, type 2 diabetes; UACR, urinary albumin to creatinine ratio.

<sup>a</sup> Excludes patients treated with eplerenone, spironolactone, any renin inhibitor, or potassium-sparing diuretic which cannot be discontinued at least 4 weeks prior to screening visit.

6.70 The financial estimates applied a percentage of 99.62% to account for patients with known significant non-diabetic renal disease, including clinically relevant renal artery stenosis, and 99.74% to account for patients on a concomitant therapy with eplerenone, spironolactone, any renin inhibitor, or potassium-sparing diuretic which could not be discontinued, based on the FIGARO-DKD and FIDELIO-DKD screening

failure logs. The ESC considered the applicability of these percentages to clinical practice uncertain and considered that a higher proportion of patients would not transition from a MRA, renin inhibitor or potassium sparing diuretic to finerenone.

6.71 The resubmission assumed that 13.98% of patients would be ineligible for treatment due to a risk of hyperkalaemia. The ESC noted that this assumption was not aligned with previous PBAC advice, that up to 58.8%-61.6% would likely be ineligible due to a risk of hyperkalaemia (based on patients who failed screening in the pivotal trials) (para 7.11, Finerenone PSD, July 2022 PBAC meeting). The ESC therefore considered that this assumption may be underestimated.

6.72 Table 18 summarises the estimated net cost of finerenone to the PBS/RPBS as presented in the resubmission.

**Table 18: Estimated use and financial implications of listing finerenone as presented in the July 2022 submission and the resubmission**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Total eligible population	1	8	8	14	14	14
Assumed uptake of finerenone	%	%	%	%	%	%
<b>Total patients treated</b>	2	6	10	12	12	12
<b>Finerenone scripts/year (11.96/patient/year)</b>	3	9	9	15	17	17
Cost of finerenone to PBS/RPBS (\$)	4	7	11	13	13	16
Patient copayment (\$17.82) (\$)	5	5	5	5	5	5
<b>Net cost to PBS/RPBS less copayment (\$)</b>	4	7	7	11	11	13
Total patients treated (July 2022)	6	10	12	8	14	19
Net cost to PBS/RPBS less copayment (July 2022) (\$)	7	11	13	16	18	20

Source: Table 116, p195 and Table 114, p196 of the resubmission; Excel Workbook 'Section\_4\_model.xlsx', Attached to the resubmission. Abbreviations: PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme; spts, scripts; yr, year.

Note: Shaded rows are uncorrected estimates from the July 2022 submission.

The redacted values correspond to the following ranges:

- <sup>1</sup> 50,000 to < 60,000
- <sup>2</sup> 10,000 to < 20,000
- <sup>3</sup> 200,000 to < 300,000
- <sup>4</sup> \$10 million to < \$20 million
- <sup>5</sup> net cost saving
- <sup>6</sup> 20,000 to < 30,000
- <sup>7</sup> \$20 million to < \$30 million
- <sup>8</sup> 60,000 to < 70,000
- <sup>9</sup> 300,000 to < 400,000
- <sup>10</sup> 30,000 to < 40,000
- <sup>11</sup> \$30 million to < \$40 million
- <sup>12</sup> 40,000 to < 50,000
- <sup>13</sup> \$40 million to < \$50 million
- <sup>14</sup> 70,000 to < 80,000
- <sup>15</sup> 400,000 to < 500,000
- <sup>16</sup> \$50 million to < \$60 million
- <sup>17</sup> 500,000 to < 600,000
- <sup>18</sup> \$60 million to < \$70 million
- <sup>19</sup> 90,000 to < 100,000
- <sup>20</sup> \$80 million to < \$90 million

6.73 As stated previously, the pre-PBAC response proposed a price reduction for finerenone (\$|AEMP). The estimated net cost of finerenone to the PBS/RPBS based on this price reduction is summarised in Table 19.

**Table 19: Estimated use and financial implications of listing finerenone as presented in the pre-PBAC response**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Total patients treated	█ <sup>1</sup>	█ <sup>3</sup>	█ <sup>5</sup>	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>
Net cost to PBS/RPBS less copayment (\$)	█ <sup>2</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>7</sup>	█ <sup>7</sup>	█ <sup>7</sup>

Source: 'Item 7.07 Pre-PBAC Response finerenone (Kerendia) Section\_4\_model revised.xlsx'. Attached to the pre-PBAC response.

The redacted values correspond to the following ranges:

<sup>1</sup> 10,000 to < 20,000

<sup>2</sup> \$0 to < \$10 million

<sup>3</sup> 20,000 to < 30,000

<sup>4</sup> \$10 million to < \$20 million

<sup>5</sup> 30,000 to < 40,000

<sup>6</sup> 40,000 to < 50,000

<sup>7</sup> \$20 million to < \$30 million

6.74 At Year 1, the estimated number of patients was 10,000 to < 20,000 and based on the price reduction proposed in the pre-PBAC response the net cost to the PBS would be \$0 to < \$10 million. At Year 6, the estimated number of patients was 40,000 to < 50,000 and the net cost to the PBS would be \$20 million to < \$30 million. This is substantially less than the July 2022 estimate of \$80 million to < \$90 million in Year 6, a total of \$200 million to < \$300 million over 6 years. This is consistent with the narrower population in the requested restriction and the price reduction proposed in the pre-PBAC response.

6.75 The estimated use and financial impact of finerenone may not be reliable due to uncertainties with key sources and parameters used to determine the size of the eligible and treated populations and are likely underestimated (see Table 17).

6.76 The resubmission stated that the listing of finerenone is not expected to impact the use of other medicines on the PBS/RPBS as it is positioned as additional therapy to current SoC, including SGLT2i medicines. The impact of the requested restriction on the use of RAASi therapies and steroidal mineralocorticoid receptor antagonists (e.g. spironolactone, eplerenone) for the treatment of comorbid heart failure and/or treatment-resistant essential hypertension, remains unclear.

6.77 The costs of monitoring and management of hyperkalaemia related to the use of finerenone was not included in the resubmission, and were considered to be part of routine patient care for CKD and T2D. The risk of finerenone related hyperkalaemia and management of hyperkalaemia events was not adequately addressed in the resubmission, and may result in increased costs to health budgets and patients. The PSCR argued that while the budget impact did not account for the additional cost of hyperkalaemia, it also did not account for cost-offsets related to improved cardiovascular and renal outcomes (e.g. reduction in dialysis) and considered the costs related to hyperkalaemia are modest in comparison to the cost savings associated with improvements to health outcomes associated with finerenone treatment. The ESC agreed with the evaluation and considered that the exclusion of a cost related to

hyperkalaemia in the financial estimates was not appropriate. The ESC also considered that the cost associated with a reduction in dialysis is largely a cost to the states and territories, not the MBS, and would therefore be inappropriate to include in the financial estimates.

6.78 Following the ESC consideration, a series of sensitivity analyses were conducted by the DUSC secretariat that amended parameters of the utilisation and cost model to be in line with those recently accepted for dapagliflozin (Table 23, dapagliflozin PSD, November 2021), including:

- SA 1: Proportion of type 2 diabetes patients with UACR  $\geq$  200 mg/g and eGFR  $\geq$  25 mL/min/1.73m<sup>2</sup> from 12.1% to 7.5%;
- SA 2: SA 1 + Proportion of patients currently on SGLT2i or intolerant/contraindicated to SGLT2i from 24.1% to 50%; and
- SA 3: SA 1 + SA 2 + Proportion of high-risk CKD patients receiving an ACEi or ARB from 72.7% to 80%.

6.79 The results of the sensitivity analyses are shown in Table 20. The estimated net cost to the PBS/RPBS for finerenone would be \$0 to < \$10 million in Year 1, increasing to \$10 million to < \$20 million in Year 6, a total of \$80 million to < \$90 million over the first 6 years of listing.

**Table 20: Sensitivity analyses of the estimated use and financial implications of listing finerenone based on the amended financial estimates provided in the pre-PBAC response**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Sensitivity analysis 1</b>						
Patients	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>4</sup>	■ <sup>4</sup>	■ <sup>4</sup>	■ <sup>4</sup>
Net cost PBS / RPBS	■ <sup>2</sup>	■ <sup>2</sup>	■ <sup>3</sup>	■ <sup>3</sup>	■ <sup>3</sup>	■ <sup>3</sup>
<b>Sensitivity analysis 2</b>						
Patients	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>4</sup>	■ <sup>4</sup>	■ <sup>5</sup>	■ <sup>5</sup>
Net cost PBS / RPBS	■ <sup>2</sup>	■ <sup>2</sup>	■ <sup>3</sup>	■ <sup>3</sup>	■ <sup>3</sup>	■ <sup>3</sup>
<b>Sensitivity analysis 3</b>						
Patients	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>4</sup>	■ <sup>5</sup>	■ <sup>5</sup>	■ <sup>5</sup>
Net cost PBS / RPBS	■ <sup>2</sup>	■ <sup>3</sup>	■ <sup>3</sup>	■ <sup>3</sup>	■ <sup>3</sup>	■ <sup>3</sup>

Source: Conducted by the DUSC secretariat. 'Item 7.07 Pre-PBAC Response finerenone (Kerendia) Section\_4\_model revised.xlsx'. Attached to the pre-PBAC response.

The redacted values correspond to the following ranges:

<sup>1</sup> 10,000 to < 20,000

<sup>2</sup> \$0 to < \$10 million

<sup>3</sup> \$10 million to < \$20 million

<sup>4</sup> 20,000 to < 30,000

<sup>5</sup> 30,000 to < 40,000

### Quality Use of Medicines

6.80 Quality use of medicines was not addressed in the resubmission. Similar to the July 2022 submission, the resubmission did not consider the potential for finerenone to

displace steroidal mineralocorticoid receptor antagonists (e.g. spironolactone, eplerenone) prescribed for other indications (e.g. reduced ejection fraction heart failure, treatment-resistant hypertension) in the target PBS population. The risk-benefit profile of finerenone in other indications is not known. Furthermore, the risk of accidental co-prescribing of finerenone for diabetic renal disease and other mineralocorticoid receptor antagonists for heart failure exists and would result in a high risk for severe hyperkalaemia.

### **Financial Management – risk sharing arrangements**

- 6.81 Overall, the ESC considered that the financial impact of finerenone may not be reliable due to the uncertainty of key sources and parameters used to estimate the size of the eligible and treated populations. The ESC considered a risk sharing arrangement (RSA) may minimise the risk due to uncertainty in the financial estimates.
- 6.82 The pre-PBAC response stated that the sponsor is willing to work with the Department of Health to finalise an RSA structure should finerenone be recommended for PBS listing.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the General Schedule Authority Required listing of finerenone for the treatment of chronic kidney disease (CKD) in patients with type 2 diabetes mellitus (diabetic kidney disease; DKD). The PBAC was satisfied that finerenone in combination with standard of care provides, for some patients, a significant improvement in efficacy over standard of care alone. The PBAC considered that finerenone has a limited place in therapy given a small and uncertain reduction in clinical events in CKD and cardiovascular disease with use in combination with standard of care, including a sodium-glucose cotransporter inhibitor (SGLT2i), and the complication of hyperkalaemia. The PBAC considered finerenone would be cost-effective based on the revised economic model assumptions and the price reduction offered in the pre-PBAC response. However, the PBAC considered that the utilisation estimates remained overestimated and should be revised to include parameters aligned with those recently accepted in the CKD setting.
- 7.2 The PBAC acknowledged the supportive comments in the clinician hearing and the consumer comments from Kidney health Australia. The PBAC shared the concern that the pill burden and risk of hyperkalaemia may limit uptake of finerenone.
- 7.3 The PBAC noted the requested restriction was revised to reflect a more limited place in therapy for use in patients with high albuminuria (urinary albumin-to-creatinine ratio (UACR) of 200 mg/g or greater), excluding patients with heart failure with reduced ejection fraction (HFrEF), and as an add-on to standard of care comprising an angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB) and SGLT2i unless contraindicated. While the UACR cut-off proposed in the

resubmission did not align with the PBAC's previous advice to only include patients with very high albuminuria of 300 mg/g or greater (paragraph 6.21, Finerenone PSD, July 2022 PBAC meeting), the PBAC considered the revised clinical criteria aligning with that of dapagliflozin in CKD was adequately justified and was acceptable.

- 7.4 The PBAC agreed with the restriction changes suggested by the Secretariat.
- 7.5 The PBAC considered that the revised comparator proposed in the resubmission of placebo in combination with standard of care, comprised of treatment with an ACEi or ARB in combination with an SGLT2i therapy (unless contraindicated or intolerant), was appropriate and consistent with previous PBAC advice (paragraph 7.4, Finerenone PSD, July 2022 PBAC meeting).
- 7.6 The PBAC recalled it had previously accepted treatment with finerenone was associated with a statistically significant reduction in composite time to first renal and first cardiovascular event compared to placebo, based on the FIDELITY pre-specified pooled analysis of the FIDELIO-DKD and FIGARO-DKD randomised trials. A claim of modestly superior efficacy was considered reasonable for the duration of the trials and the broader trial populations, and it was further noted that the composite risk of renal events in the individual trials was driven by a reduction in patients experiencing a sustained  $\geq 40\%$  relative decrease in eGFR from baseline, rather than a reduction in renal failure or renal death (paragraph 7.6, Finerenone PSD, July 2022 PBAC meeting). The PBAC also considered that the magnitude of benefit for patients receiving an SGLT2i was uncertain due to the small number of patients in the clinical trials receiving this class of drug (paragraph 7.7, Finerenone PSD, July 2022 PBAC meeting). The PBAC noted the resubmission provided *post hoc* subgroup analyses of the FIDELITY pooled data, for patients with a UACR > 200 mg/g, with or without concomitant treatment with an SGLT2i medicine, and the incidence of hyperkalaemia by baseline UACR and eGFR (presented in Table 6). The PBAC considered that although the patient numbers for concomitant treatment with an SGLT2i were small and therefore the outcomes of the *post hoc* analyses remained uncertain, it was accepted that these analyses were supportive of a similar magnitude of benefit in the more restricted population compared to the overall ITT population in FIDELITY.
- 7.7 The PBAC considered the revised claim of inferior safety compared to placebo was reasonable and consistent with previous PBAC advice, which noted finerenone treatment was associated with an increased number of treatment-related adverse events and adverse events leading to discontinuation, in particular a significant increase in hyperkalaemia (paragraph 7.8, Finerenone PSD, July 2022 PBAC meeting).
- 7.8 The PBAC noted that in response to ESC advice the updated economic model provided in the pre-PBAC response increased the treatment discontinuation probabilities based on CKD stage and applied equal rates of progression from CKD 5 to dialysis in both arms of the model (hazard ratio [HR] = 1). The PBAC considered that these conservative amendments to the model provided more appropriate base case assumptions of long-term treatment effect. The PBAC noted the price reduction

proposed in the pre-PBAC response (\$| AEMP to \$| AEMP) was also more in line with the price of dapagliflozin and, on balance, finerenone was likely to be cost-effective in the DKD setting at the revised ICER of \$5,000 to < \$15,000/QALY gained.

- 7.9 The PBAC noted the revised financial implications from the pre-PBAC response remained unreasonably high, despite the lower price offer being more aligned with dapagliflozin. The PBAC considered that the parameters for calculating the financial implications of listing finerenone should be amended to reflect those recently accepted in the CKD setting for dapagliflozin (see paragraphs 6.78–6.79). The PBAC noted the lower patient numbers and the lower financial implications over 6 years of forward estimates based on the revisions provided by the DUSC secretariat (see Table 20). The PBAC considered the revised utilisation estimates provided by the DUSC secretariat in sensitivity analysis 3 were likely to be a more accurate reflection of the extent of use of finerenone in a later line treatment setting to dapagliflozin.
- 7.10 The PBAC considered that a risk sharing arrangement was appropriate in the context of an uncertain patient population. The PBAC considered that the revised financial estimates as presented in Table 20 would be a reasonable basis for subsidisation caps with 10% rebate above the caps.
- 7.11 The PBAC recommended that finerenone should not be treated as interchangeable on an individual patient basis with any other drugs.
- 7.12 The PBAC advised that finerenone is suitable for prescribing by nurse practitioners as continuing therapy only.
- 7.13 The PBAC recommended that the Early Supply Rule should not apply.
- 7.14 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway were not met. Specifically the PBAC found that in the circumstances of its recommendation for finerenone:
- a) The treatment is expected to provide a moderate improvement in efficacy over standard of care on the basis of the clinical evidence considered at the July 2022 and March 2023 meetings;
  - b) The treatment is not expected to address a high and urgent unmet clinical need;
  - c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 7.15 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

Add new indication as follows:

MEDICINAL PRODUCT medicinal product pack		PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
FINERENONE						
finerenone 10 mg tablet, 28		NEW	1	28	5	Kerendia
finerenone 20 mg tablet, 28		NEW	1	28	5	Kerendia
<b>Restriction Summary / Treatment of Concept:</b>						
Concept ID (for internal Dept. use)	<b>Category / Program:</b> GENERAL – General Schedule (Code GE)					
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners					
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (Streamlined) [new code]					
Prescribing rule level	<b>Administrative Advice:</b> For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.					
	<b>Condition:</b> Chronic kidney disease with Type 2 diabetes					
<b>Indication:</b> Chronic kidney disease with Type 2 diabetes						
<b>Clinical criteria:</b>						
Patient must have a diagnosis of chronic diabetic kidney disease, defined as abnormalities of at least one of: (i) kidney structure, (ii) kidney function, present for at least 3 months, prior to initiating treatment with this drug,						
<b>AND</b>						
<b>Clinical criteria:</b>						
Patient must not have known significant non-diabetic renal disease, prior to initiating treatment with this drug.						
<b>AND</b>						
<b>Clinical criteria:</b>						
Patient must have an estimated glomerular filtration rate of 25 mL/min/1.73 m <sup>2</sup> or greater, prior to initiating treatment with this drug						
<b>AND</b>						
<b>Clinical criteria:</b>						
Patient must have a urinary albumin-to-creatinine ratio of 200 mg/g (22.6 mg/mmol) or greater, prior to initiating treatment with this drug						
<b>AND</b>						
<b>Clinical criteria:</b>						
Patient must discontinue treatment with this drug prior to initiating renal replacement therapy, defined as dialysis or kidney transplant,						
<b>AND</b>						
<b>Clinical criteria:</b>						
Patient must be stabilised, for at least 4 weeks, on either: (i) an ACE inhibitor or (ii) an angiotensin II receptor antagonist, unless medically contraindicated, prior to initiation of combination therapy with this drug.						
<b>AND</b>						
<b>Clinical criteria:</b>						
The treatment must be in combination with an SGLT2i unless medically contraindicated or intolerant.						

	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must not be receiving treatment with another selective nonsteroidal mineralocorticoid-receptor antagonist, a renin inhibitor or a potassium-sparing diuretic.
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must not have established heart failure with reduced ejection fraction with an indication for treatment with a mineralocorticoid receptor antagonist.
	<b>Caution:</b>
	Serum electrolytes should be checked regularly

***This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.***

## **9 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **10 Sponsor's Comment**

Bayer welcomes the PBAC's recommendation of finerenone for PBS listing for the treatment of chronic kidney disease (CKD) in patients with type 2 diabetes mellitus (diabetic kidney disease; DKD). We continue to work with the Department to have finerenone available on the PBS at the earliest opportunity.