

## 6.06 EMPAGLIFLOZIN, Tablet 10 mg, Jardiance<sup>®</sup>, Boehringer Ingelheim Pty Ltd.

### 1 Purpose of submission

- 1.1 The Category 2 submission requested a General Schedule Authority Required (STREAMLINED) listing for empagliflozin for the treatment of chronic kidney disease (CKD).
- 1.2 Listing was requested on the basis of a cost minimisation versus dapagliflozin (both in combination with standard care) and a cost-effectiveness analysis versus placebo (both in combination with standard care).

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

Component	Description
Population	Adult patients with chronic kidney disease with eGFR 20 to <45 mL/min/1.73 m <sup>2</sup> or eGFR 45 to <90 mL/min/1.73 m <sup>2</sup> with UACR ≥200 mg/g.
Intervention	Empagliflozin 10 mg once daily (add-on to standard care)
Comparator	Dapagliflozin (add-on to standard care) in patients with CKD with eGFR 25 to 75 mL/min/1.73 m <sup>2</sup> and UACR of 200 to 5,000 mg/g (overlap population). Placebo (add-on to standard care) in patients with CKD with eGFR 20 to <45 mL/min/1.73 m <sup>2</sup> or eGFR 45 to <90 mL/min/1.73 m <sup>2</sup> with UACR ≥200 mg/g, who do not meet the biomedical criteria for dapagliflozin (incremental population) <sup>a</sup> .
Outcomes	Composite of kidney disease progression and cardiovascular death, all-cause mortality, hospitalisation for heart failure, all-cause hospitalisation, kidney disease progression, cardiovascular death, composite of cardiovascular death or Stage 5 CKD, annual rate of change in eGFR, sustained decline in eGFR, quality of life and adverse events.
Clinical claim	Empagliflozin (add-on to standard care) is noninferior in terms of efficacy and safety compared to dapagliflozin (add-on to standard care), in the overlap population. Empagliflozin (add-on to standard care) is superior in terms of efficacy and noninferior in terms of safety compared to placebo (add-on to standard care), in the incremental population.

Source: Table 1.2, p19 of the submission.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; UACR, urine albumin-creatinine ratio.

<sup>a</sup> Incremental population includes patients with an eGFR 75 to <90 mL/min/1.73m<sup>2</sup> with UACR ≥200 mg/g, or 25 to 75 mL/min/1.73m<sup>2</sup> with UACR >5,000 mg/g, or 25 to <45 mL/min/1.73m<sup>2</sup> with UACR <200 mg/g, or 20 to <25 mL/min/1.73m<sup>2</sup> regardless of UACR.

Note: Standard care includes treatment with an ACEi or an ARB to reduce proteinuria and cardiovascular risk.

### 2 Background

#### Registration status

- 2.1 TGA status at time of PBAC consideration: The submission was made under the TGA/PBAC Parallel Process. The positive TGA Delegate's overview was received on 31 October 2023. It is anticipated that empagliflozin will be considered at the 1 December 2023 ACM meeting, and the Delegate's decision available on 12 January 2024. The proposed TGA indication is:

For the treatment of adults with chronic kidney disease, to reduce the risk of kidney disease progression (sustained decline in estimated glomerular filtration rate (eGFR), end-stage kidney disease or renal death) or cardiovascular death, and all-cause hospitalisation.

- 2.2 During the evaluation, the TGA Clinical Evaluation Report became available, with the recommendation the indication be amended as follows:

For the treatment of adult patients with chronic kidney disease, as an adjunct to standard of care therapy, to reduce the risk of kidney disease progression.

- 2.3 In addition, the TGA Clinical Evaluation Report requested justification of the use of a sustained decline of  $\geq 40\%$  in eGFR in the composite primary endpoint in the EMPA-KIDNEY trial; a sustained decline of  $\geq 50\%$  in eGFR was used in the composite primary endpoint of the DAPA-CKD trial. The sponsor was also requested to provide the data/justification which led to the acceptance of the broader CKD indication in the European Union, particularly the benefits in less advanced CKD patients.

- 2.4 The TGA Delegate advised that overall, the submitted data and subsequent responses by the sponsor support following extension of indication:

JARDIANCE is indicated in adult patients with chronic kidney disease to reduce the risk of kidney disease progression.

- 2.5 Empagliflozin was approved by the FDA in November 2022, to reduce the risk of sustained decline in eGFR, end stage kidney disease (ESKD), renal death, cardiovascular death, and all-cause hospitalisation in adults with CKD. The EMA extended the indication for empagliflozin to include the treatment of adult CKD patients on 22 June 2023.

### ***Previous PBAC consideration***

- 2.6 Empagliflozin is listed on the PBS:

- For the treatment of type 2 diabetes mellitus (T2DM) in combination with metformin and/or a sulfonylurea, or in combination with insulin, or in combination with metformin and a gliptin.
- For the treatment of adults with symptomatic NYHA class II, III, or IV chronic heart failure with a left ventricular ejection fraction  $\leq 40\%$ , as an adjunct to standard care.

- 2.7 At the December 2022 meeting, the PBAC recommended extending the existing listing of empagliflozin to include the treatment of chronic heart failure in patients with a left ventricular ejection fraction  $>40\%$  (para 12.1, Empagliflozin Public Summary Document (PSD), November 2022 PBAC meeting and December 2022 addendum). This recommendation was not PBS listed at the time of evaluation.

### 3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
EMPAGLIFLOZIN					
Empagliflozin 10 mg tablet, 30	\$61.01	1	30	5	Jardiance
<b>Category / Program:</b> 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>Indication:</b> Chronic kidney disease					
<b>Clinical criteria:</b>					
Patient must have a diagnosis of chronic 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 have an estimated glomerular filtration rate of at least 20 mL/min/1.73 m <sup>2</sup> but less than 90 mL/min/1.73 m <sup>2</sup> prior to initiating treatment with this drug,					
<b>AND</b>					
<b>Clinical criteria:</b>					
If the patient has an estimated glomerular filtration rate of at least 45 mL/min/1.73 m <sup>2</sup> but less than 90 mL/min/1.73 m <sup>2</sup> , the patient must have a urinary albumin to creatinine ratio of at least 200 mg/g (22.6 mg/mmol) 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 not be receiving treatment with another sodium-glucose co-transporter 2 (SGLT2) inhibitor.					
<b>Prescribing Instructions:</b> Patient must be treated with either: (i) an ACE inhibitor or (ii) an angiotensin II receptor antagonist, unless not tolerated or not medically indicated, prior to initiation of combination therapy with this drug.					
<b>Prescribing Instructions:</b> Patients with polycystic kidney disease; patients with a recent history of intravenous immunosuppressive therapy; and patients currently receiving immunosuppressive therapy comprising of at least 45 mg prednisolone (or equivalent) are not eligible for treatment with this drug.					
<b>Administrative Advice:</b>					
Note Continuing Therapy Only: 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 Practitioner					

Note: The DPMQ was corrected during the evaluation. The submission proposed 60 days' supply to reflect the PBS 60 day dispensing program. Empagliflozin is not an eligible stage one medicine for 60 day dispensing from 1 September 2023. There are no treatments for CKD currently recommended for 60 day dispensing (<https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2022-12/Increased-Dispensing-Quantities-List-of-Medicines.pdf>).

- 3.1 The submission requested a dispensed price for empagliflozin 10 mg of \$108.18 (DPMQ per 2 packs of 30 tablets) assuming 60 day dispensing and an AEMP of \$44.66 (1 pack of 30 tablets). The requested AEMP (\$44.66) is consistent with the PBS listed AEMP of empagliflozin for the treatment of diabetes and chronic heart failure. Given empagliflozin is not an eligible stage one medicine for 60 day dispensing, the requested DPMQ was corrected during the evaluation (\$61.01) to reflect a maximum quantity of 1 pack (30 tablets) dispensed, updated for current mark-ups at 1 July 2023.

- 3.2 The requested restriction is narrower than the proposed TGA indication and limits subsidised treatment with empagliflozin for CKD to patients with biomedical markers consistent with the inclusion criteria of the key clinical trial (EMPA-KIDNEY) on initiation.
- 3.3 The requested restriction is based on the current PBS listing for dapagliflozin for the treatment of CKD, encompassing the Australian population eligible for PBS subsidised dapagliflozin (eGFR 25 to 75 mL/min/1.73 m<sup>2</sup> with urine albumin-creatinine ratio (UACR) 200 to 5,000 mg/g). The requested restriction also includes additional patients with similarly impaired kidney function (eGFR 25 to 75 mL/min/1.73 m<sup>2</sup> and UACR >5,000 mg/g; eGFR 25 to 45 mL/min/1.73 m<sup>2</sup> and UACR <200 mg/g), more severely impaired kidney function (eGFR 20 to <25 mL/min/1.73 m<sup>2</sup> regardless of albuminuria), and less severely impaired kidney function (eGFR 75 to <90 mL/min/1.73 m<sup>2</sup> and UACR ≥200 mg/g). The ESC considered there will potentially be confusion amongst prescribers given the different PBS eligibility between the SGLT2 inhibitors, however the ESC advised against expanding the dapagliflozin restriction to match the proposed empagliflozin restriction given it would be outside the available trial evidence for dapagliflozin.
- 3.4 In addition, the requested restriction does not exclude patients with CKD related to lupus nephritis or anti-neutrophil cytoplasmic antibody related vasculitis (excluded from the dapagliflozin restriction) and only requires treatment with an ACE inhibitor or ARB without the requirement to be stabilised on treatment for at least 4 weeks (included in the dapagliflozin restriction). The pre-PBAC response indicated the sponsor would accept the same restriction wording as the current dapagliflozin CKD listing should the PBAC make a positive recommendation to enable a PBS listing for empagliflozin to proceed for the currently reimbursed CKD population. The response suggested this would enable an alternative SGLT2 inhibitor to be available for patients with a high clinical need for treatment and allow prescribers choice of SGLT2 inhibitor based on individual patient characteristics.

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

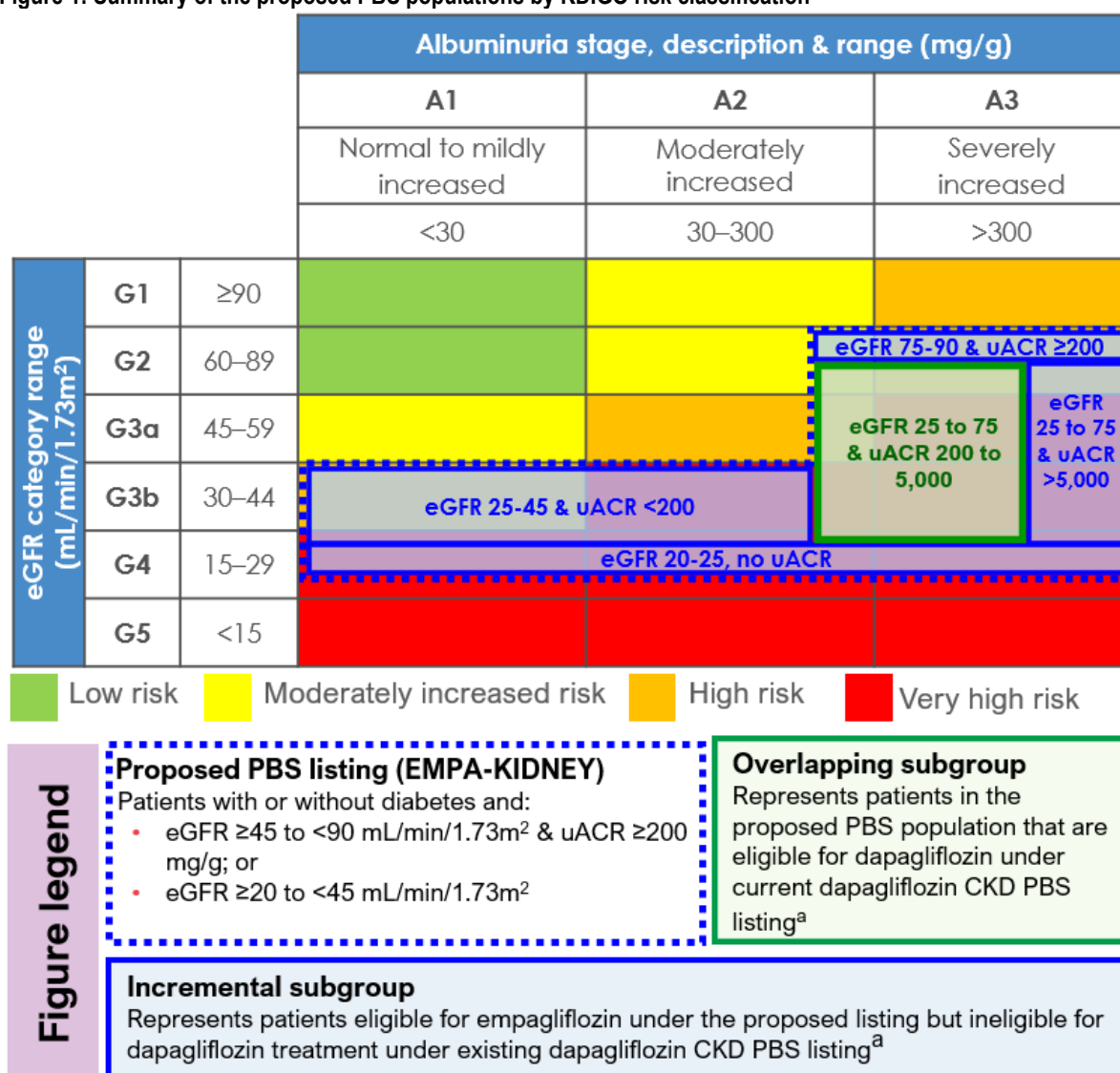
## **4 Population and disease**

- 4.1 CKD is characterised by the gradual loss of kidney function over time as a natural consequence of ageing, *both reversible and irreversible* causes (e.g. diabetic nephropathy, polycystic kidney disease, auto immune disease, recurrent kidney/urinary infection and scarring) and related risk factors (e.g. diabetes, hypertension, cardiovascular disease, obesity, prior acute kidney injury, family history of kidney disease, smoking, age >60 years, Aboriginal and Torres Strait Islander descent; Kidney Health Australia 2020).
- 4.2 CKD is defined as having an estimated or measured glomerular filtration rate (eGFR) of <60 mL/min/1.73 m<sup>2</sup> that is present for 3 months or more with or without evidence of kidney damage, and/or evidence of kidney damage (albuminuria, haematuria,

structural abnormalities, pathological abnormalities) with or without a decrease in eGFR, present for 3 months, irrespective of underlying cause (Kidney Health Australia 2020, CKD Management in Primary Care).

- 4.3 The current prevalence of CKD in the Australian population is not known, but available data based on a single biological measurement suggest that approximately one in three Australian adults are at risk of developing CKD, one in ten have early signs of disease and up to 1.7 million may be living with undiagnosed CKD (National Health Measurement Survey NHMS 2011-2012). Approximately 10% of the Australian population with biomedical signs of CKD will be diagnosed, given diagnosis is typically delayed until progression to CKD stage 3-4 disease when symptoms of kidney disease are more apparent (AIHW 2023). The severity of CKD and the risk of progression to Stage 5 CKD or cardiovascular death can be assessed using the Kidney Disease Improving Global Outcomes (KDIGO) classification of CKD prognosis.
- 4.4 Figure 1 describes the proposed population in terms of KDIGO risk classification.

Figure 1: Summary of the proposed PBS populations by KDIGO risk classification



Source: Figure 1.1, p17 of the submission.

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; PBS, Pharmaceutical Benefits Scheme; SC, standard care; UACR, urine albumin to creatinine ratio.

<sup>a</sup> Dapagliflozin PBS listing for the treatment of CKD (PBS item 13106T).

4.5 The overlap population includes patients enrolled in the EMPA-KIDNEY trial who would be eligible for PBS subsidised treatment with dapagliflozin for CKD (based on baseline eGFR and UACR). As per paragraph 3.4, the population also includes patients not eligible for dapagliflozin treatment by other criteria (CKD related to lupus nephritis or anti-neutrophil cytoplasmic antibody related vasculitis; prior RAS therapy stabilised over 4 weeks). The ESC considered it would be appropriate to align these aspects of the dapagliflozin and empagliflozin restrictions.

4.6 The incremental population includes a broad amalgam of patients with substantially variable eGFR and UACR characteristics, and baseline risk of CKD progression. The

incremental population was not sufficiently homogenous to be considered suitable for reliable subgroup analyses (see paras 6.25 to 6.30 below).

- 4.7 Empagliflozin is a selective sodium-glucose co-transporter-2 (SGLT2) inhibitor widely used for the treatment of adults with T2DM. The precise mechanisms of action underlying the protective cardiovascular and renal effects of empagliflozin are not completely understood, but several mechanisms of action have been proposed for SGLT2 inhibitors (Seferovic et al. 2020; Figure 1.1.3, Attachment 1 of the commentary), and these actions are thought to be independent of the glycaemic effects of SGLT2 inhibitors.
- 4.8 The recommended dose of empagliflozin for the treatment of CKD is empagliflozin 10 mg orally, once daily, adjunctive to standard care (including treatment with an ACE inhibitor or ARB). The empagliflozin 25 mg strength was not requested in the submission, as both empagliflozin dose strengths were found to be equally effective in patients with T2DM in slowing eGFR decline in subgroup analyses conducted for the EMPA-REG OUTCOME trial.
- 4.9 The proposed clinical management algorithm positions empagliflozin as an adjunctive therapy to standard care with an ACE inhibitor or ARB, as an alternative SGLT2 inhibitor to dapagliflozin, and as an SGLT2 inhibitor treatment option for patients in a broader CKD population not eligible for PBS subsidised dapagliflozin.
- 4.10 The NPS MedicineWise practice guideline criteria for use of SGLT2 inhibitor medicines in CKD (2022), and UK Kidney Association Clinical Practice Guidelines (2021) are derived from the inclusion criteria of the key dapagliflozin clinical trial (DAPA-CKD) and are consistent with the similarly derived dapagliflozin PBS listing and dapagliflozin Product Information.
- 4.11 A recent meta-analysis of the use of SGLT2 inhibitors for the treatment of kidney outcomes supported a class effect of SGLT2 inhibitors in reducing the risk of kidney disease progression, acute kidney injury, cardiovascular death, and hospitalisation for heart failure in patients with CKD (Nuffield et al. 2022).

## **5 Comparator**

- 5.1 The submission nominated dapagliflozin (add-on to standard care) and placebo (add-on to standard care) as the main comparators. The submission argued that dapagliflozin is the appropriate comparator for the overlap population of CKD patients eligible for PBS subsidised dapagliflozin (CKD with an eGFR of  $\geq 25$  to  $\leq 75$  mL/min/1.73 m<sup>2</sup> and a UACR of  $\geq 200$  to  $\leq 5,000$  mg/g). For other patients eligible for treatment with empagliflozin, the incremental population, placebo is the appropriate comparator (see Table 2 below).

**Table 2: Proposed comparators for the PBS populations**

Population ID	Population criteria	Comparators <sup>a</sup>
Overlap population <sup>b</sup>	- eGFR 25 to 75 mL/min/1.73m <sup>2</sup> with UACR 200 to 5,000 mg/g.	Dapagliflozin (add-on to SC).
Incremental population <sup>c</sup>	- eGFR 75 to <90 mL/min/1.73m <sup>2</sup> with UACR ≥200 mg/g. - eGFR 25 to 75 mL/min/1.73m <sup>2</sup> with UACR >5,000 mg/g. - eGFR 25 to <45 mL/min/1.73m <sup>2</sup> with UACR <200 mg/g. - eGFR 20 to <25 mL/min/1.73m <sup>2</sup> regardless of UACR.	Placebo (add-on to SC).

Source: Table 1.1, p18 of the submission.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; ITT, intention-to-treat; SC, standard care; UACR, urine albumin to creatinine ratio.

<sup>a</sup> Standard care consists of treatment with either an ACEi or an ARB.

<sup>b</sup> Based on the biomedical criteria of the Dapagliflozin PBS listing for the treatment of CKD (PBS item 13106T).

<sup>c</sup> An amalgam of the biomedical criteria of all other eligible patients not otherwise eligible for treatment with dapagliflozin.

- 5.2 The recommended dosing and administration of empagliflozin and dapagliflozin are similar, and unlikely to impact use in the eligible populations. However, there are differences in the recommended use and precautions in patients with impaired kidney function. The dapagliflozin Product Information states that initiating treatment with dapagliflozin in patients with eGFR <25 mL/min/1.73 m<sup>2</sup> is not recommended, and the glucose lowering efficacy of dapagliflozin is reduced in patients with eGFR <45 mL/min/1.73 m<sup>2</sup>. The current empagliflozin Product Information states that empagliflozin should not be used in patients with T2DM with severe renal impairment (eGFR <30 mL/min/1.73m<sup>2</sup>). The proposed empagliflozin Product Information removes the precautions and contraindications related to use of the empagliflozin 10 mg dose in patients with eGFR <30 mL/min/1.73 m<sup>2</sup> for T2DM and <20 mL/min/1.73 m<sup>2</sup> for heart failure and recommends that empagliflozin 10 mg can be used regardless of renal function, but due to limited experience, is not recommended in patients on dialysis.
- 5.3 The TGA Clinical Evaluator noted that empagliflozin should not be used in patients with eGFR <20 mL/min/1.73 m<sup>2</sup> and considered that dose recommendations for CKD patients based on results in the EMPA-KIDNEY trial should not automatically apply to patients with T2DM and heart failure.

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

## 6 Consideration of the evidence

### **Sponsor hearing**

- 6.1 There was no hearing for this item.

### **Consumer comments**

- 6.2 The PBAC noted and welcomed the input from individuals (3), and organisations (3) via the Consumer Comments facility on the PBS website. The comments from patients who would like to access the medicine and those caring for an individual with CKD described the expected benefits of treatment with empagliflozin included slowing progression of the disease, improving quality of life, and reducing the need for dialysis and transplant.

- 6.3 The PBAC noted the input from hearts4heart described the benefits of the proposed listing for empagliflozin providing treatment for a broader population of high-risk CKD patients that do not have PBS access to a SGLT2 inhibitor and have limited alternative treatment options. The expanded population was noted to include patients with very poor kidney function without proteinuria, patients with very high proteinuria, and patients with rarer causes of CKD such as IgA nephropathy and ANCA-associated vasculitis. These high-risk patient populations may lack access to effective treatments.
- 6.4 The PBAC noted the input from Kidney Health Australia described benefits of slowing progression of disease and delaying the time to requiring dialysis or transplantation, providing hope to both the clinicians and their patients. Comments further described that data arising from trials using empagliflozin in kidney disease have shown benefit across a wide range of eGFR and proteinuria levels. In particular, benefit was shown for those that had a preserved eGFR with proteinuria and those with a low eGFR without proteinuria. Both these groups currently are limited in available therapies and are yet highly vulnerable populations.
- 6.5 The PBAC noted the National Aboriginal Community Controlled Health Organisation (NACCHO) described the increased disease burden and mortality associated with CKD for Aboriginal and Torres Strait Islander peoples. The ACCHO sector has been strongly advocating for wider access to SGLT-2 inhibitors due to benefits of reduced proteinuria, reduced progression to CKD 5 and cardiovascular mortality benefit. Patients may not meet PBS eligibility criteria, such as can't be combined with GLP-1 agonists when used for diabetes or not having all recent pathology data available. For example, dapagliflozin for CKD requires urine ACR: 22.6 – 565 mg/mmol, pathology may not be available or can exclude patients with CKD grade 1 and multiple other risk factors for progression. NACCHO would like to propose removing this barrier by listing on PBS for Aboriginal and Torres Strait Islander peoples with CKD, without reference to other clinical criteria, to allow clinician discretion.
- 6.6 The PBAC noted and appreciated the need for effective therapies in this disease, however it considered the evidence provided in the submission did not adequately support the benefits of expanding access for empagliflozin in CKD to include a broader population than is currently eligible for dapagliflozin.

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

### **Clinical trials**

- 6.7 The submission was based on discrete comparisons for the overall eligible population, overlap population, and incremental population.
- Overall eligible population: based on one randomised controlled trial of patients with CKD (EMPA-KIDNEY), comparing empagliflozin to placebo (both in addition to standard care).

- Incremental population: based on *post hoc* subgroup analyses of the EMPA-KIDNEY trial incremental population (excluding patients in the overlap population) comparing empagliflozin to placebo (both in addition to standard care).
- Overlap population: based on an indirect comparison of empagliflozin (EMPA-KIDNEY) to dapagliflozin (DAPA-CKD), with placebo as the common reference. Analyses included indirect comparisons using the EMPA-KIDNEY overall population and *post hoc* subgroup analyses of the EMPA-KIDNEY overlap population.

6.8 Details of the trials presented in the submission are provided in Table 3 below.

**Table 3: Trials presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Empagliflozin trials</b>		
EMPA-KIDNEY	A multicentre international randomized parallel group double-blind placebo-controlled clinical trial of empagliflozin once daily to assess cardio-renal outcomes in patients with chronic kidney disease.  Herrington WG, Staplin N, Wanner C, et al. Empagliflozin in patients with chronic kidney disease.  Herrington WG, Preiss D, Haynes R, et al. The potential for improving cardio-renal outcomes by sodium-glucose co-transporter-2 inhibition in people with chronic kidney disease: a rationale for the EMPA-KIDNEY study.  Herrington WG, Wanner C, Green JB, et al. Design, recruitment, and baseline characteristics of the EMPA-KIDNEY trial.	Clinical Study Report, 28 October 2022.  New England Journal of Medicine 2023; 388(2):117-127.  Clinical Kidney Journal 2018; 11(6):749-761.  Nephrology Dialysis Transplantation 2022; 37(7):1317-1329.
<b>Dapagliflozin trials</b>		
DAPA-CKD	Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease.  Wheeler DC, Stefánsson BV, Jongs N, et al. The dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD) trial: baseline characteristics.	New England Journal of Medicine 2020; 383:1436-1446.  Nephrology Dialysis Transplant 2020; 35(10):1700-1711.

Source: Table 2.1, p71 and Table 2A.1, pp184-185 of the submission.

6.9 The PBAC previously considered the DAPA-CKD trial for the treatment of patients with CKD at the July, September and November 2021 meetings (Dapagliflozin PSD, July 2021 PBAC meeting with September 2021 Addendum and November 2021 Addendum) and March 2022 meeting (Dapagliflozin PSD, March 2022 PBAC meeting).

6.10 The key features of the 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 model
EMPA-KIDNEY	6,609	R, DB, PC, MC 12 months	Low	Adults with CKD and eGFR 20 to <45 mL/min/1.73 m <sup>2</sup> or eGFR 45 to <90 mL/min/1.73 m <sup>2</sup> with UACR ≥200 mg/g, treated with standard care of ACEi/ARB unless intolerant	Primary composite outcome: ≥40% decline in eGFR, eGFR <10 mL/min/1.73 m <sup>2</sup> , ESKD, or CV death. Secondary outcomes: all-cause mortality, CV mortality, ESKD, other renal/cardiovascular outcomes and safety.	<i>Post hoc</i> subgroup analyses by KDIGO category
DAPA-CKD	4,304	R, DB, PC, MC 24 months	Low	Adults with CKD and eGFR 25 to ≤75 mL/min/1.73 m <sup>2</sup> with UACR 200-5,000 mg/g, treated with maximum tolerated dose of ACEi/ARB for ≥4 weeks, unless contraindicated	Primary composite outcome: ≥50% decline in eGFR, ESKD, CV or renal death. Secondary outcomes: all-cause mortality, CV mortality, ESKD, hospitalisation for HF; other renal/cardiovascular composite outcomes and safety.	-

Source: Constructed during the evaluation

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; CV, cardiovascular; DB, double blind; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HF, heart failure; MC, multi-centre; PC, placebo controlled; R, randomised; UACR, urine albumin-creatinine ratio

- 6.11 The EMPA-KIDNEY trial was an event driven study planned to continue until a minimum of 1,070 primary outcome events had occurred. The trial was terminated early for benefit based on predefined stopping criteria. The median duration of follow-up was 24.33 months.
- 6.12 There were substantial differences between the incremental, overlap and overall populations across most demographic and disease characteristics. Patients in the incremental population were older (mean age 66.8 years) compared to the overlap population (mean age 58.7 years) and overall population (mean age 63.3 years), and included smaller proportions of males (incremental: 63.1%, overlap: 71.9%, overall: 66.8%), patients of Asian descent (26.9%, 48.4%, 36.2%), and smokers (8.5%, 12.7%, 10.3%). In addition, the incremental population included a smaller proportion of patients with glomerular based kidney disease (15.8%, 37.7%, 25.3%), and larger proportions of patients with T2DM (49.0%, 38.4%, 44.4%), and prior cardiovascular disease (32.0%, 19.7%, 26.7%). A smaller proportion of patients in the incremental population was categorised as very high risk of kidney disease progression (64.9%, 87.7%, 74.7%).
- 6.13 The majority of patients in the overlap population reported baseline UACR >300 mg/g (79.2% in the KDIGO G3aA3, G3bA3, G4A3 categories). In the incremental population, there were large proportions of patients in the KDIGO G3bA1-A2 and G4A1-A3 risk categories, consistent with the complement of the overlap population; with very small numbers of patients in the G2A2-A3, G3aA1-A3 and G3bA3 risk categories. The incremental population included a broad amalgam of patients with substantially

variable baseline risk of CKD progression, heavily weighted by patients with a baseline eGFR <45 mL/min/1.73 m<sup>2</sup>. Notwithstanding the small numbers of patients in some KDIGO categories (G2A2-A3, G3aA2-A3 and G3bA3), the incremental population may not be sufficiently homogenous for subgroup analysis.

- 6.14 Patient demographic characteristics were similar between the EMPA-KIDNEY and DAPA-CKD trial, but there were substantial differences in terms of CKD disease severity and kidney disease progression. The EMPA-KIDNEY trial included a larger proportion of patients with eGFR <30 mL/min/1.73 m<sup>2</sup> (34.5%) compared to DAPA-CKD (14.5%), and a smaller proportion of patients with baseline UACR >300 mg/g (51.7% versus 89.7%). Smaller proportions of patients in the EMPA-KIDNEY trial had T2DM (44.4% versus 67.5%) and cardiovascular disease (27% versus 37%) compared to DAPA-CKD, and fewer were treated with ACE inhibitors or ARBs (85% versus 98%). The ESC considered that the effect of these differences in baseline characteristics on the overall trial results was uncertain, but as the differences appeared bidirectional, then any overall effect on the ITT population was likely small, but could be more significant in the subgroup results.
- 6.15 Similar to the EMPA-KIDNEY trial, the DAPA-CKD trial was event driven, and was terminated early due to findings of positive efficacy on interim results. The median duration of follow-up in the DAPA-CKD trial was 2.4 years (range 2.0 to 2.7 years), similar to EMPA-KIDNEY (median 24.33 months).
- 6.16 The submission compared the characteristics of patients in the EMPA-KIDNEY trial with an Australian retrospective cohort study of the MedicinesInsight database, which included a cohort matching the biomedical inclusion criteria (eGFR, UACR) of the EMPA-KIDNEY trial (Neuen 2023). Based on the comparison, the EMPA-KIDNEY trial population was younger (63.3 years) than the Australian population (74.4 years), included a higher proportion of males (66.8% versus 50.9%), a higher proportion with eGFR <30 mL/min/1.73 m<sup>2</sup> (34.5% versus 9.1%), and a higher proportion with UACR >300 mg/g (51.7% versus 35.6%). In the EMPA-KIDNEY trial, 74.7% of patients were in the very high risk KDIGO category, compared to 20.2% of patients in the Australian cohort.

## **Comparative effectiveness**

### ***Overall population***

- 6.17 Table 5 summarises the results of the primary composite outcome of CKD progression or adjudicated cardiovascular death in the EMPA-KIDNEY trial.

**Table 5: Results for the primary composite outcome CKD progression or adjudicated cardiovascular death in EMPA-KIDNEY (ITT)**

	<b>Empagliflozin + SC N=3,304</b>	<b>Placebo + SC N=3,305</b>	<b>Hazard ratio (95% CI)</b>
<b>Primary composite outcome</b>			
CKD progression or CV death, n (%)	432 (13.1%)	558 (16.9%)	<b>0.72 (0.64, 0.82)</b>
<b>Components</b>			
CKD progression first event, n (%)	384 (11.6%)	504 (15.2%)	-
- ESKD, n (%)	47 (1.3%)	63 (1.9%)	
- eGFR reduced <10 mL/min/1.73 m <sup>2</sup> and ≥40%	43 (1.3%)	67 (2.0%)	
- eGFR reduced to 10 mL/min/1.73 m <sup>2</sup>	1 (<0.1%)	1 (<0.1%)	
- eGFR reduction ≥40% only	293 (8.9%)	373 (11.3%)	
CV death first event, n (%)	48 (1.5%)	54 (1.6%)	

Source: Table 2.13, pp103-104 of the submission.

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; ITT, intention-to-treat; NR, not reported; SC, standard care.

Note: Statistically significant results in bold.

6.18 Treatment with empagliflozin plus standard care was associated with a statistically significant improvement in the composite outcome of time to first CKD progression or cardiovascular death compared to placebo plus standard care, over a median duration of follow-up of 24.33 months. This difference was primarily driven by a reduction in CKD progression in patients experiencing a sustained ≥40% relative decrease in eGFR from baseline (2.4% of the overall difference of 3.8% in the primary composite outcome).

6.19 Table 6 summarises the results of key secondary outcomes in the EMPA-KIDNEY trial.

**Table 6: Results for key secondary outcomes in EMPA-KIDNEY (ITT)**

<b>Outcome</b>	<b>Empagliflozin + SC N=3,304</b>	<b>Placebo + SC N=3,305</b>	<b>Hazard ratio (95% CI)</b>
Time to first CKD progression, n (%)	384 (11.6)	504 (15.2)	<b>0.71 (0.62, 0.81)</b>
Time to first adjudicated CV death, n (%)	59 (1.8)	69 (2.1)	0.84 (0.60, 1.19)
Time to adjudicated all-cause mortality, n (%)	148 (4.5)	167 (5.1)	0.87 (0.70, 1.08)
Time to all-cause hospitalisation, n (%)	840 (25.4)	899 (27.2)	<b>0.86 (0.75, 0.98)</b>
Total hospitalisations (first and recurrent), n	1,611	1,895	NA

Source: Table 2.14, p107, Table 2.16, p110, Table 2.17, p111, and Table 2.18, p113 of the submission.

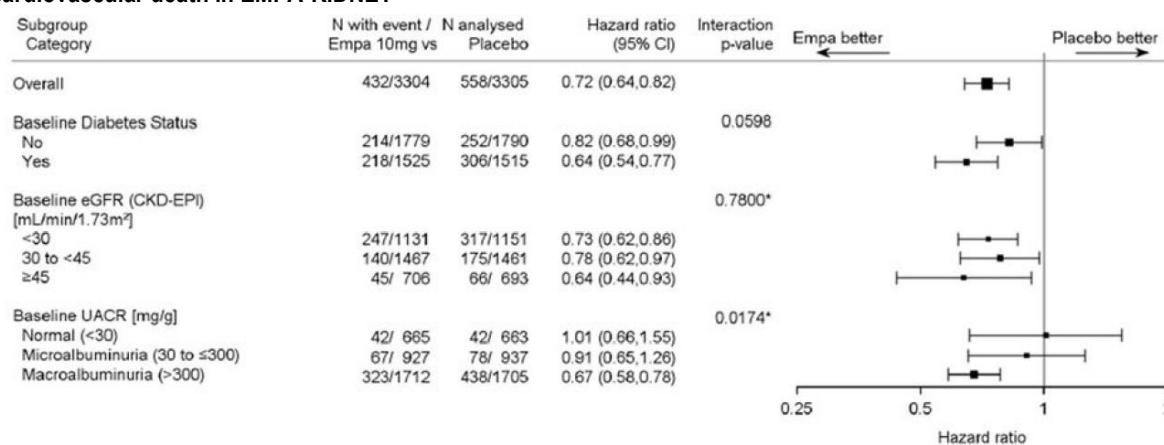
Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; CI, confidence interval; ITT, intention-to-treat; NA, not applicable; SC, standard care.

Note: Statistically significant results in bold.

6.20 Treatment with empagliflozin plus standard care was associated with statistically significant improvements in the outcomes of time to first CKD progression, and time to all cause-hospitalisation compared to placebo. Treatment with empagliflozin was also associated with nominal improvements in all-cause mortality and cardiovascular mortality compared to placebo, but differences between treatment arms did not achieve statistical significance. Given the short duration of the EMPA-KIDNEY trial (median duration of 24.33 months) and early termination, long term mortality outcomes may not have been informed by sufficiently mature data to capture differences between treatment arms, and should be interpreted with caution.

- 6.21 Treatment with empagliflozin plus standard care was associated with a statistically significant improvement in the secondary composite outcome of time to first adjudicated cardiovascular death or ESKD compared to placebo plus standard care (HR 0.73, 95% CI 0.59, 0.89), and was associated with a numerical improvement in the composite of hospitalisation for heart failure or adjudicated cardiovascular death compared to placebo, but the difference did not reach statistical significance.
- 6.22 The annual rate of change in eGFR was assessed for the period from baseline to the final follow-up (total slope) and the period from Month 2 to final follow-up. The submission argued that the total slope analysis is biased against empagliflozin due to non-linearity in the empagliflozin arm resulting from the initial dip in eGFR followed by a stabilisation of eGFR decline (see Figure 2.12, p116 of the submission; EMPA-KIDNEY CTR 11.1.3.1.2: 1 p106); a pattern observed in other SGLT2 inhibitor trials, including the dapagliflozin CKD trial (DAPA-CKD; Figure 3, p1,444 Heerspink 2020). Both analyses showed less eGFR decline in patients treated with empagliflozin versus placebo, however, the difference was more favourable for the difference in decline in eGFR from Month 2 to final follow-up (1.37 mL/min/1.73 m<sup>2</sup> per year, 95% CI 1.16, 1.59) than from baseline to final follow-up (0.75 mL/min/1.73 m<sup>2</sup> per year, 95% CI 0.54, 0.96). There was a substantial decline in eGFR in the empagliflozin treatment arm between baseline and Month 2. The impact of the SGLT2 inhibitor group effect on kidney function (i.e. decline in eGFR) in patients with poor kidney function on initiation of empagliflozin (i.e. <30 mL/min/1.73 m<sup>2</sup>) is unclear. The ESC advised that it would be important for clinicians to monitor renal function carefully in this high-risk subgroup after commencing patients on an SGLT2 inhibitor.
- 6.23 EQ-5D-5L values and VAS scores were collected during the EMPA-KIDNEY trial from baseline to follow-up. EQ-5D index scores were not reported, however there were no relevant treatment differences in the descriptive analyses across the treatment groups in the scores of the EQ-5D questionnaire.
- 6.24 As shown in Figure 2 below, pre-specified subgroup analyses for the primary composite outcome of CKD progression or cardiovascular death in the EMPA-KIDNEY trial showed significant treatment effect interaction by baseline diabetes status (p=0.0598) and albuminuria subgroups (UACR<30, 30-300, and >300 mg/g; p=0.0174), with a trend of decreasing treatment effect in patients without diabetes or with a lower baseline UACR (UACR ≤300 mg/g).

Figure 2: Results of the pre-specified subgroup analysis for primary composite outcome of CKD progression or cardiovascular death in EMPA-KIDNEY



Source: Figure 2.19, p136 of the submission.

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; Empa, empagliflozin; EPI, epidemiology collaboration formula; UACR, urine albumin to creatinine ratio.

### Overlap and incremental populations

6.25 Table 7 summarises the results of the *post hoc* subgroup analyses of the overlap and incremental populations and KDIGO baseline risk categories for the primary composite outcome of CKD progression or cardiovascular death in the EMPA-KIDNEY trial.

**Table 7: Results of the post hoc overlap and incremental subgroup analysis and KDIGO baseline risk categories for the primary composite outcome CKD progression or CV death in EMPA-KIDNEY (ITT)**

Population or subgroup	eGFR (mL/min/1.73 m <sup>2</sup> )	UACR (mg/g)	Empagliflozin + SC n/N (%)	Placebo + SC n/N (%)	Hazard ratio (95% CI)
<b>Pre-specified subgroup analyses</b>					
ITT	20 to <45 45 to <90	NA ≥200	432/3305 (13.1%)	558/3304 (16.9%)	<b>0.72 (0.64, 0.82)</b>
Overlap	25 to 75	200-5,000	184/1446 (12.7%)	227/1397 (16.2%)	<b>0.76 (0.63, 0.92)</b>
Incremental	20 to <25 25 to <45 25 to 75 >75 to <90	NA <200 >5,000 ≥200	248/1858 (13.3%)	331/1908 (17.3%)	<b>0.76 (0.65, 0.90)</b>
<b>Post hoc subgroup analyses<sup>a</sup></b>					
G2A1	60 to 89	<30	-	-	-
G2A2		30-300	1/55 (1.8%)*	1/43 (2.3%)*	NR*
G2A3		>300	14/175 (8.0%)*	16/188 (8.5%)*	0.83 (0.40, 1.69)*
G3aA1	45 to 59	<30	-	-	-
G3aA2		30-300	5/112 (4.5%)*	5/111 (4.5%)*	NR*
G3aA3		>300	20/256 (7.8%)*	40/260 (15.4%)*	<b>0.47 (0.27, 0.80)*</b>
G3bA1	30 to 44	<30	19/389 (4.9%)*	15/400 (3.8%)*	1.40 (0.71, 2.77)*
G3bA2		30-300	33/442 (7.5%)*	36/454 (7.9%)*	0.93 (0.58, 1.49)*
G3bA3		>300	88/636 (13.8%)*	124/607 (20.4%)*	<b>0.67 (0.51, 0.88)*</b>
G4A1	15 to 29	<30	21/196 (10.7%)*	23/189 (12.2%)*	0.88 (0.49, 1.59)*
G4A2		30-300	28/308 (9.1%)*	36/327 (11.0%)*	0.85 (0.52, 1.40)*
G4A3		>300	193/618 (31.2%)*	253/627 (40.4%)*	<b>0.69 (0.57, 0.84)*</b>

Source: Table 2.26, p133 of the submission; Table 1.1.2.2, pp19-22 of Att\_4\_EMPA-KIDNEY post hoc analysis B.pdf, Attachment 4 to the submission.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; ITT, intention-to-treat; NA, not applicable; NR, not reported; SC, standard care; UACR, urine albumin to creatinine ratio.

<sup>a</sup> Based on a Cox regression model with terms for age (p<0.0001), sex (p=0.1812), baseline diabetes status (p<0.0001), region (p=0.0431), treatment (p=0.3867), baseline KDIGO risk (p=0.0039) and treatment by baseline KDIGO risk, interaction (p=0.5521).

Note: Statistically significant results in bold.

\* Note that the results presented in Table 7 are derived from post-hoc analyses conducted by the applicant. These analyses were not part of the pre-specified statistical plan for EMPA-KIDNEY. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.26 Treatment with empagliflozin plus standard care was associated with statistically significant improvements in the composite outcome of time to first CKD progression or cardiovascular death compared to placebo plus standard care, in both the overlap and incremental populations, and showed a similar magnitude of effect to the ITT population (interaction p-value=0.990). Given the subgroup analyses were conducted post hoc, the results should be interpreted with caution. Subgroup analyses by the incremental population subgroups (eGFR 75 to <90 mL/min/1.73m<sup>2</sup> with UACR ≥200 mg/g; eGFR 25 to 75 mL/min/1.73m<sup>2</sup> with UACR >5,000 mg/g; eGFR 25 to <45 mL/min/1.73m<sup>2</sup> with UACR <200 mg/g; eGFR 20 to <25 mL/min/1.73m<sup>2</sup> regardless of UACR) were not presented.

6.27 However, in the post hoc subgroup analyses by KDIGO risk categories, empagliflozin showed mixed results in the primary composite outcome, and only achieved statistically significant improvements compared to placebo in patients with baseline macroalbuminuria (KDIGO risk categories G3aA3, G3bA3, G4A3), recognising that subgroup sizes were small and not powered for the composite endpoint.

- 6.28 Post hoc subgroup analyses were presented in Section 3 of the submission for annual change in eGFR and relative change in UACR from baseline to 18 months by KDIGO baseline risk categories.
- 6.29 Treatment with empagliflozin was associated with a statistically significant reduction in the annual rate of eGFR decline compared to placebo in the EMPA-KIDNEY trial. However, there were statistically significant treatment effect interactions by baseline KDIGO category ( $p=0.0023$ ), with the largest treatment effects observed in patients with baseline UACR  $>300$  mg/g.
- 6.30 Treatment with empagliflozin was associated with statistically significantly better UACR ratios (more improvement/less worsening) compared to placebo in the EMPA-KIDNEY trial. However, there were statistically significant treatment effect interactions by baseline KDIGO category ( $p=0.0054$ ), with the largest treatment effects observed in patients with baseline UACR  $>300$  mg/g and patients with UACR  $>30$  mg/g who have significant renal impairment (eGFR 15 to  $<30$ ; 30 to  $<45$  mL/min/1.73 m<sup>2</sup>).

***Indirect comparison of empagliflozin versus dapagliflozin***

- 6.31 Table 8 summarises the results of the indirect comparison of empagliflozin with dapagliflozin (with placebo as the common reference) for the primary composite outcome of CKD progression or adjudicated cardiovascular death. Results of the indirect comparison were presented using the results of the EMPA-KIDNEY overlap population, as well as the EMPA-KIDNEY ITT population.
- 6.32 There were small differences in the definitions of kidney disease progression between the EMPA-KIDNEY and DAPA-CKD trials in terms of ESKD (EMPA-KIDNEY: initiation of maintenance dialysis or kidney transplant; DAPA-CKD: chronic dialysis or kidney transplant) and sustained decline in eGFR (EMPA-KIDNEY: sustained decline in eGFR to  $<10$  mL/min/1.73 m<sup>2</sup> or  $\geq 40\%$ ; DAPA-CKD:  $<15$  mL/min/1.73 m<sup>2</sup> or  $\geq 50\%$ ). Results of the indirect comparison were reported using native trial outcome definitions, as well as the DAPA-CKD outcome definitions applied to EMPA-KIDNEY patient data *post hoc*.

**Table 8: Results of the indirect comparison of empagliflozin versus dapagliflozin for the primary composite outcome of time to CKD progression or CV death (placebo + SC as common reference)**

	Empagliflozin + SC events n/N (%)	Placebo + SC Events n/N (%)	Dapagliflozin + SC events n/N (%)	Hazard ratio (95% CI)
<b>Indirect comparison based on EMPA-KIDNEY definition of primary outcome applied to EMPA-KIDNEY data<sup>a</sup></b>				
EMPA-KIDNEY (ITT)	432/3,304 (13.1%)	558/3,305 (16.9%)	-	<b>0.72 (0.64, 0.82)</b>
EMPA-KIDNEY (overlap)	119/1,446 (8.2%)	227/1,397 (16.2%)	-	<b>0.76 (0.63, 0.92)</b>
DAPA-CKD (ITT)	-	312/2,152 (14.5%)	197/2,152 (9.2%)	<b>0.61 (0.51, 0.72)</b>
<b>Indirect comparisons:</b>	Empagliflozin + SC (ITT) vs dapagliflozin + SC			1.18 (0.96, 1.46)
	Empagliflozin + SC (overlap) vs dapagliflozin + SC			1.25 (0.96, 1.61)
<b>Indirect comparison based on DAPA-CKD definition of primary outcome applied to EMPA-KIDNEY data<sup>b</sup></b>				
EMPA-KIDNEY (ITT DAPA-CKD)	381/3,304 (11.5%)	494/3,305 (14.9%)	-	<b>0.71 (0.62, 0.82)</b>
EMPA-KIDNEY (overlap DAPA-CKD)	119/1,446 (8.2%)	152/1,397 (10.9%)	-	<b>0.74 (0.58, 0.94)</b>
DAPA-CKD (ITT)	-	312/2,152 (14.5%)	197/2,152 (9.2%)	<b>0.61 (0.51, 0.72)</b>
<b>Indirect comparisons:</b>	Empagliflozin + SC (ITT DAPA-CKD definition) vs dapagliflozin + SC			1.16 (0.93, 1.45)
	Empagliflozin + SC (overlap DAPA-CKD definition) vs dapagliflozin + SC			1.21 (0.90, 1.63)

Source: Table 2A.17, p226 and Table 2A.18, p227 of the submission.

Abbreviations: CI, confidence interval; CV, cardiovascular; ESKD, end-stage kidney disease; ITT, intention-to-treat; SC, standard care; UACR, urine albumin-creatinine ratio.

<sup>a</sup> Primary composite outcome of DAPA-CKD (CKD progression as a sustained decline in eGFR of  $\geq 50\%$  from baseline, or ESKD including a sustained eGFR to  $< 15$  mL/min/1.73 m<sup>2</sup> chronic dialysis treatment or renal transplant, renal death, or CV death) differed from EMPA-KIDNEY (CKD progression as a sustained decline in eGFR of  $\geq 40\%$  from baseline or  $< 10$  mL/min/1.73 m<sup>2</sup>, or ESKD, or CV death).

<sup>b</sup> Post hoc EMPA-KIDNEY results based on the DAPA-CKD definition of primary composite outcome.

Note: Statistically significant results in bold.

- 6.33 Treatment with empagliflozin plus standard care showed no statistically significant difference compared to dapagliflozin plus standard care for the composite outcome of time to first CKD progression or cardiovascular death for all indirect comparisons. However, results of all indirect comparisons nominally favoured dapagliflozin.
- 6.34 The submission argued that the clinical claim of noninferiority could be based on a lack of statistically significant difference between treatments, as no noninferiority margin has been identified for the primary efficacy outcomes of the dapagliflozin and empagliflozin CKD trials, and the PBAC and ESC previously considered that less importance should be placed on noninferiority margins when there is a known class effect (para 6.15, Empagliflozin (hFrEF) PSD, November 2021 PBAC meeting). The ESC considered that the trial results showed comparable outcomes between dapagliflozin and empagliflozin, but that noninferiority was not convincingly established based on the differences in point estimates and the lack of a nominated noninferiority margin. The ESC considered the small differences in efficacy are potentially explained by differences in the trial populations which had different risk profiles.
- 6.35 The ESC was concerned that the lower risk incremental subgroup (by KDIGO classification) of eGFR 75 to  $< 90$  mL/min/1.73m<sup>2</sup> and UACR  $\geq 200$  mg/g (G2A2-3) had very small numbers of patients and a significantly lower treatment benefit in this group could not be excluded. This could have implications for interpretation of cost-effectiveness of the incremental subgroup.

## Comparative harms

6.36 Table 9 summarises the proportions of patients reporting key adverse events in the EMPA-KIDNEY trial. Adverse events reported were limited to serious adverse events (SAEs) and pre-specified non-serious adverse events of special interest. The proportions of patients experiencing any adverse event were not reported.

**Table 9: Summary of key adverse events in EMPA-KIDNEY (treated set)**

	<b>Empagliflozin + SC N=3,304</b>	<b>Placebo + SC N=3,305</b>
Any pre-specified non-serious adverse event <sup>a</sup> , n (%)	1,447 (43.8%)	1,520 (46.0%)
- Drug related adverse event, n (%)	79 (2.4%)	60 (1.8%)
- Discontinuation of treatment due to adverse event, n (%)	232 (7.0%)	241 (7.3%)
Serious adverse event <sup>b</sup> , n (%)	1,088 (32.9%)	1,167 (35.3%)
- Serious adverse event resulting in hospitalisation, n (%)	852 (25.8%)	937 (28.4%)
- Serious adverse event resulting in death, n (%)	88 (2.7%)	93 (2.8%)
Deaths, n (%)	126 (3.8%)	135 (3.8%)

Source: Table 2.22, p120 of the submission.

Abbreviations: SC, standard care.

<sup>a</sup> Pre-specified non-serious adverse events included adverse events resulting in discontinuation of study treatment, bone fractures, severe hypoglycaemia, gout, symptomatic dehydration, events leading to amputation, and any adverse event of special interest (serious liver disease, ketoacidosis, lower limb amputations).

<sup>b</sup> Serious adverse events defined as events that resulted in death, were life-threatening, required hospitalisation resulted in persistent or significant disability or incapacity, resulted in congenital anomaly or birth defect, or were considered important by local Investigators. Serious adverse events according with the European Medicines Agency initiative on Important Medical Events were included.

- 6.37 The proportions of patients reporting pre-specified non-serious adverse events and serious adverse events were similar between treatment arms.
- 6.38 The most commonly reported pre-specified adverse events included gout (empagliflozin 8.2%, placebo 9.2%), bone fracture (3.7%, 3.2%), volume depletion (3.0%, 2.7%), symptomatic dehydration (2.4%, 2.1%), and hypoglycaemia (2.1%, 2.0%). The most commonly reported serious adverse events were acute kidney injury (empagliflozin 2.8%, placebo 3.5%), serious hyperkalaemia (2.6%, 2.9%), and serious hypoglycaemia (2.2%, 2.2%).
- 6.39 Adverse events in the post hoc overlap and incremental populations were similar to the EMPA-KIDNEY overall population.
- 6.40 The indirect comparisons of safety outcomes presented in the submission for empagliflozin versus dapagliflozin were difficult to interpret and not reliable, given differences in the coding of adverse events between the EMPA-KIDNEY and DAPA-CKD trials.
- 6.41 The safety outcomes reported in the EMPA-KIDNEY trial were consistent with the outcomes reported in the EMPA-REG OUTCOME (cardiovascular), EMPEROR-Reduced (heart failure) and EMPEROR-Preserved (heart failure) trials and recent Periodic Benefit-Risk Evaluation Report (PBRER). The PBRER listed important identified risks of complicated urinary tract infection, genital infection and diabetic ketoacidosis with atypical presentation, and important potential risks of urinary tract carcinogenicity, liver injury, amputation and pancreatitis.

- 6.42 At the November 2021 meeting, the PBAC considered that a claim that empagliflozin was noninferior to dapagliflozin in terms of safety in the treatment of chronic heart failure with reduced ejection fraction was reasonable, and this was consistent with the long experience in clinical practice for this class of medicines (para 7.8, Empagliflozin (hFrEF) PSD, November 2021 PBAC meeting). At the November 2022 meeting, the PBAC considered that the safety profile of empagliflozin was well understood due to its use in other indications, and accepted the claim that empagliflozin was noninferior to placebo in terms of safety in the treatment of chronic heart failure with preserved ejection fraction (para 7.7, Empagliflozin (hFpEF) PSD, November 2022 PBAC meeting).

### ***Benefits/harms***

- 6.43 On the basis of the direct evidence presented in the EMPA-KIDNEY trial, for every 100 patients with CKD treated with empagliflozin in addition to standard care in comparison with standard care alone, over a median of 24 months:
- Approximately 4 fewer patients would experience CKD progression ( $\geq 40\%$  decline in kidney function, or progression to ESKD) or death related to cardiovascular causes.
  - Approximately 2 fewer patients would experience a serious adverse event.

### ***Clinical claim***

- 6.44 For the overlap population, the submission described empagliflozin plus standard care as noninferior in efficacy and noninferior in safety compared to dapagliflozin plus standard care for the treatment of CKD in adult patients. The ESC considered that it was more appropriate to conclude that empagliflozin was comparable to dapagliflozin in efficacy and safety. This was based on trial population differences between DAPA-CKD and EMPA-KIDNEY, noting that all indirect comparisons numerically favoured dapagliflozin.
- 6.45 For the incremental population, the submission described empagliflozin plus standard care as superior in efficacy and noninferior in safety compared to placebo plus standard care for the treatment of adult patients with CKD. The ESC considered the following issues should be considered:
- Uncertainty regarding the absolute magnitude of effect in clinical practice given substantial differences between the EMPA-KIDNEY trial population (including the overall, overlap and incremental populations) and the eligible population in the Australian setting. The trial included a relatively young population, with a high proportion of males and large proportions with severely increased albuminuria (UACR  $>300$  mg/g) and/or substantial renal impairment (eGFR  $<30$  mL/min/1.73 m<sup>2</sup>). In contrast, many of the patients eligible for treatment under the proposed PBS listing will be older, with a more balanced gender mix, and less advanced kidney disease.

- The incremental population was comprised of a broad range of subpopulations with different baseline UACR and eGFR levels, and included patients with both higher and lower risk than the overlap population. Given the heterogeneous nature of the incremental population, it is likely the absolute magnitude of benefit associated with empagliflozin will vary substantially across these subpopulations. The ESC was particularly concerned about the lower risk subgroup (based on KDIGO classification) of eGFR 75 to <90mL/min/1.73m<sup>2</sup> and UACR ≥200g/mg, where the magnitude of benefit may be substantially smaller, but there were insufficient patients in this subgroup to allow for meaningful comparison.
- 6.46 In addition, the EMPA-KIDNEY trial identified a statistically significant treatment effect interaction based on UACR levels which suggested that the population most likely to benefit from empagliflozin treatment was patients with high albuminuria at baseline (UACR >300 mg/g).
- 6.47 The PBAC considered that for the comparison with dapagliflozin, in the overlap population, the claim of non-inferior comparative effectiveness was reasonable.
- 6.48 The PBAC considered that for the comparison with dapagliflozin, in the overlap population, the claim of non-inferior comparative safety was reasonable.
- 6.49 The PBAC considered that for the comparison with placebo, in the incremental population, the claim of superior comparative effectiveness was not adequately supported by the data.
- 6.50 The PBAC considered that for the comparison with placebo, in the incremental population, the claim of non-inferior comparative safety was reasonable.

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

### **Economic analysis**

- 6.51 Separate economic analyses were presented in the submission for the two nominated comparators for empagliflozin for the treatment of chronic kidney disease:
- a cost-minimisation approach comparing empagliflozin with dapagliflozin in the overlap population (patients with chronic kidney disease with eGFR 25 to 75 mL/min/1.73 m<sup>2</sup> and UACR 200 to 5,000 mg/g).
  - a cost-utility analysis comparing empagliflozin plus standard care with standard care alone in patients with chronic kidney disease with eGFR 45 to <90 mL/min/1.73 m<sup>2</sup> with UACR ≥200 mg/g, or eGFR 20 to <45 mL/min/1.73 m<sup>2</sup> regardless of UACR (the combined overlap and incremental population). A scenario analysis based on the baseline characteristics of the incremental population included patients who meet the eligibility criteria for dapagliflozin for CKD, patients with diabetes and heart failure who may meet the PBS criteria for SGLT2 inhibitors for these conditions, and patients outside of the requested empagliflozin population. The ESC noted that this analysis did not include any patients from 2 of the 4 component subgroups of the incremental population

(eGFR >75 to <90 mL/min/1.73 m<sup>2</sup> and UACR ≥200 mg/g; eGFR 25 to 75 mL/min/1.73 m<sup>2</sup> and UACR >5000 mg/g).

**Cost-minimisation approach**

- 6.52 The submission presented a cost-minimisation approach for empagliflozin versus dapagliflozin in adult CKD patients with eGFR 25 to 75 mL/min/1.73 m<sup>2</sup> and UACR 200 to 5,000 mg/g.
- 6.53 The equi-effective doses were estimated as empagliflozin 10 mg once daily and dapagliflozin 10 mg once daily, consistent with recommended doses in the Product Information and doses used in the EMPA-KIDNEY and DAPA-CKD trials, respectively.
- 6.54 The submission noted that the difference in pack sizes between empagliflozin (30 days of treatment) and dapagliflozin (28 days) means that dapagliflozin treated patients would require additional visits to the GP to obtain a new original prescription. To incorporate this difference, the cost-minimisation approach was conducted over 12 months and included the additional resource use and cost (offsets) associated with GP visits. The ESC noted that factoring in GP costs for 30 days versus 28 days is an unnecessary complication that has not been considered in previous CMAs for SGLT2 inhibitors.
- 6.55 The cost minimisation approach was based on the assumption that 60 day dispensing would apply to both empagliflozin and dapagliflozin. This was not reasonable, as treatments for chronic kidney disease are not currently recommended for 60 day dispensing. During the evaluation the submission's cost-minimisation approach was re-calculated using the same methodology but with current dispensing durations, updated to reflect July 2023 fees and mark-ups.
- 6.56 Results of the cost-minimisation (as calculated during the evaluation based on 28/30 day dispensing) are presented in Table 10.

**Table 10: Results of the cost-minimisation approach proposed in the submission and calculated during the evaluation**

Component	Value (calculation)
<b>Dapagliflozin</b>	
Published AEMP	\$41.69
Prescriptions per year	13.045 (=365.25/28 days per script)
Total cost of medicine	\$543.83 (= \$41.69 × 13.045)
Cost of GP visits for prescribing	\$41.20 (MBS item #23)
GP visits per year	2.174 (=365.25/[28 days × 6 scripts (1 initial & 5 repeats)])
Total cost of GP visits	\$89.57 (= \$41.20 × 2.174)
<b>Total cost of treatment</b>	<b>\$633.40 (= \$543.83 + \$89.57)</b>
<b>Total cost of treatment without GP visits</b>	<b>\$543.83 (medicine costs only)</b>
<b>Empagliflozin</b>	
<b>Total cost of treatment</b>	<b>\$633.40</b>
Cost of GP visits for prescribing	\$41.20 (MBS item #23)
GP visits per year	2.029 (=365.25/[30 days × 6 scripts (1 initial & 5 repeats)])
Total cost of GP visits	\$83.60 (= \$41.20 × 2.029)
Total cost of medicine	\$549.80 (= \$633.40 - \$83.60)
Prescriptions per year	12.175 (=365.25 /30 days per script)
<b>Derived AEMP</b>	<b>\$45.16 (= \$549.80 /12.175)</b>
<b>Derived AEMP without GP visits</b>	<b>\$44.67 <sup>1</sup>(= \$543.83/12.175)</b>

Source: Table 2A.4, p342 of the submission, modified during the evaluation to conform with current dispensing durations and with MBS Item 23 costs at 1 July 2023.

Abbreviations: AEMP, approved ex-manufacturer price; GP, general practitioner

6.57 The AEMP for empagliflozin derived from the submission's cost-minimisation approach using 60 day dispensing (\$) was not consistent with the AEMP proposed in Section 1 of the submission and used in the submission's cost-utility analysis and financial estimates (\$89.32, which is the AEMP for a 30 day prescription (\$44.66) multiplied by 2), or the current AEMP (\$44.66) for other empagliflozin PBS listings. The AEMP for empagliflozin derived during the evaluation (\$45.16), using the submission's cost-minimisation approach with 30 day dispensing instead of 60 day dispensing, was also inconsistent with the AEMP of \$44.66. Without consideration of GP visits, the cost-minimised price of empagliflozin was consistent with the existing AEMP. The ESC considered the approach without GP visits was consistent with previous CMA decisions for the SGLT2 inhibitors in other indications and was the most appropriate option.

### **Cost utility approach**

6.58 The submission presented a modelled economic evaluation of empagliflozin plus standard care versus standard care alone based on clinical data from the overall EMPA-KIDNEY population, with additional modelled data.

6.59 The submission also presented a scenario analysis using modelled baseline characteristics of the incremental population, based on clinical data from the overall EMPA-KIDNEY population, with additional modelled data.

6.60 The economic evaluations were presented as cost-effectiveness/cost-utility analyses.

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

Table 11: Key components of the economic evaluation

Component	Summary
Treatments	Empagliflozin and placebo (both in combination with an ACE inhibitor and an ARB)
Time horizon	20 years in the model base case versus mean follow-up of 23.9 months in EMPA-KIDNEY.
Outcomes	ESKD; CV death; life years; quality adjusted life years
Methods used to generate results	Microsimulation of 1000 patients. To obtain stable results, the randomness around patient characteristics and risks were fixed to a specific seed.
Health states	15 CKD health states defined by KDIGO classification categories (G2A1 to G5A3), non-CVD, non-renal death. The model also includes a number of submodules including ESKD (including renal death), cardiovascular disease (including CVD death), acute kidney injury, hypertension, diabetes and adverse events.
Cycle length	1 year
Transition probabilities	<p>Treatment discontinuations were separately estimated for each treatment arm based on data from the overall population of the EMPA-KIDNEY trial. Patients initiating renal replacement therapy (RRT) are also assumed to discontinue treatment.</p> <p>Disease progression was based on independently modelled changes in eGFR and UACR. eGFR progression was based on a <i>post hoc</i> analysis of annual change in eGFR based on KDIGO categories from EMPA-KIDNEY while patients remain on treatment; then modelled based on a US prospective observational cohort study of disease trajectories in patients with chronic renal insufficiency (Grams 2021). UACR change over time was based on a <i>post hoc</i> analysis of annual change in UACR based on KDIGO categories from EMPA-KIDNEY while patients remain on treatment; then modelled based on a meta-analysis of individual patient data from published cohort studies reporting longitudinal data on albuminuria/proteinuria and the subsequent risk of ESKD (Coresh 2019). Patients transition to another health state when their eGFR and/or UACR crosses a threshold for a different KDIGO classification health state, based on change in eGFR and UACR within a cycle.</p> <p>The change in other risk factors (HbA1c, BMI, SBP) while on treatment was based on data from the EMPA-KIDNEY trial. The change in risk factors while off-treatment and/or for treatment independent risk factors (HDL, TC) were based on various published sources (Wilson 1993, Leal 2021, Pani 2008, Iyanden 2021, Zaninotto 2019).</p> <p>Progression to ESKD occurs when a patient's eGFR falls below 15 mL/min/1.73 m<sup>2</sup> (informed by modelled eGFR and UACR progression). The risk of RRT (dialysis or transplant) was based on a published international risk equation (Tangri 2016). The distribution between dialysis types (haemodialysis and peritoneal dialysis) and kidney transplant was based on an <i>ad hoc</i> analysis of ANZDATA data in patients initiating RRT in 2020. Transitions between RRTs and death were based on treatment status at 1 year from the same ANZDATA analysis. Patients who do not receive RRT receive conservative care. The model included risks of complications from peritoneal dialysis (based on Perl 2020) and haemodialysis (based on Dalgaard 2015 and Culp 1995).</p> <p>The risk of diabetes (Hippisley-Cox 2017), hypertension (Vidal-Petiot 2018), cardiovascular events (Matsushita 2020, D'Agostino 2000, Wolf 1991, Eriksson 2001, EMPA-REG OUTCOME), peripheral artery disease (Cea-Soriano 2018, Matsushita 2017), heart failure (Grams 2021), acute kidney injury (Sawhney 2017, James 2015, Hatakeyama 2017) and amputation (EMPA-KIDNEY) were based on various published sources including multiple risk equations and assumptions. The model included additional treatment effects of empagliflozin on heart failure and acute kidney injury based on the EMPA-KIDNEY trial.</p> <p>Age- and sex-specific non-cardiovascular, non-renal mortality rates in the Australian population were based on ABS life tables (2019-2021), adjusted to remove the proportion of deaths due to ischaemic heart disease, cerebrovascular disease and renal failure based on AIHW General Record of Incidence of Mortality (GRIM 2020).</p> <p>Death due to kidney disease occurs in ESKD patients only. Death in patients on RRT was based on all-cause deaths in patients receiving dialysis or transplant from ANZDATA. Patients in ESKD receiving conservative care die if their eGFR reaches <math>\leq 3</math> mL/min/1.73 m<sup>2</sup>.</p> <p>The risk of cardiovascular disease mortality was estimated based on a published risk equation that estimated risk based on eGFR, albuminuria levels and other risk factors (Matsushita 2020).</p>

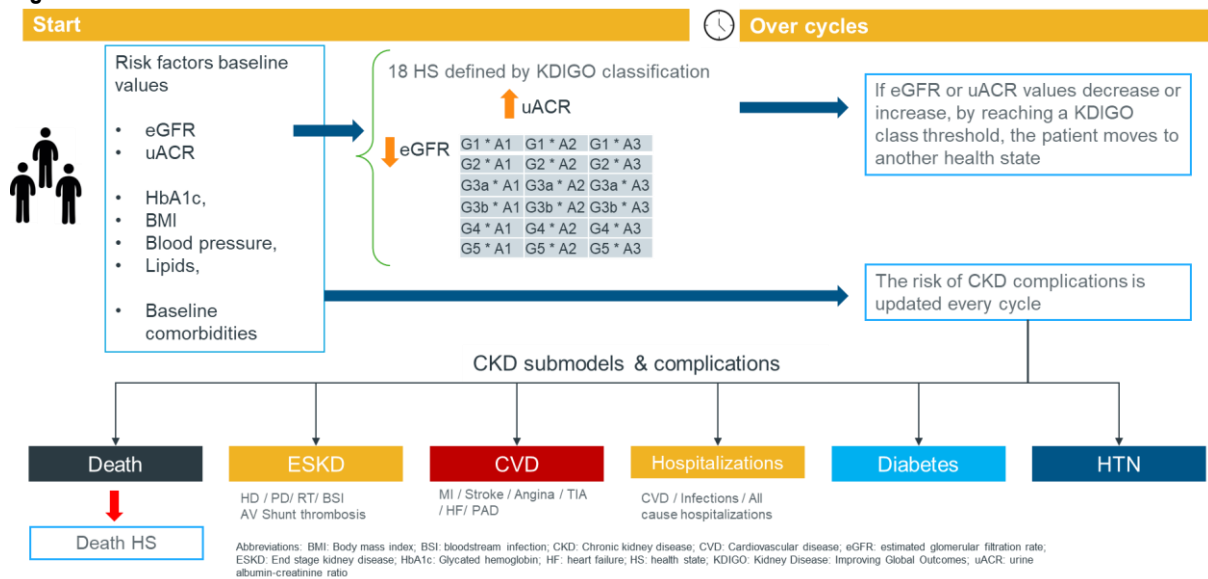
Component	Summary
Utility values	<p>Pre-ESKD health state utilities by KDIGO category (G2A1 to G4A3) were based on a <i>post hoc</i> subgroup analysis of EQ-5D-5L data from the EMPA-KIDNEY trial, mapped to EQ-5D-3L and valued using the UK value set.</p> <p>The ESKD (conservative care) utility was based on Jesky 2016, a prospective observational cohort study of UK patients with pre-dialysis CKD which used EQ-5D-3L to collect quality of life data.</p> <p>Utilities for dialysis were based on the average utilities for haemodialysis and peritoneal dialysis from a systematic review of utilities derived using EQ-5D in patients receiving RRT (Liem 2008).</p> <p>The utility for kidney transplant was based on the estimate from the July 2021 dapagliflozin submission, derived from a utility study in patients from a hospital renal unit in Wales using the EQ-5D (Lee 2005).</p> <p>Disutilities associated with MI, unstable angina, stroke and heart failure hospitalisation were based on a study assessing the impact of diabetes-related complications on EQ-5D utility scores in patients with type 2 diabetes using data from the UKPDS (Clarke 2002). The transient ischaemic attack disutility was based on SF-12 responses from a nationally representative US survey, mapped to EQ-5D-3L (Sullivan 2016). The peripheral artery disease disutility was based on a cross-sectional survey of European type 2 diabetes patients using the EQ-5D (Bagust and Beale 2005).</p> <p>The disutility associated with acute kidney injury was based on SF-12 responses from a nationally representative US survey, mapped to EQ-5D-3L (Sullivan 2016).</p> <p>Disutilities for amputation adverse events were not included.</p>
Costs	<p>Empagliflozin costs were based on the proposed DPMQ, based on 60 day dispensing, with perfect adherence assumed.</p> <p>The costs of standard care were based on the assumption that patients receive both an ACE inhibitor and ARB, assuming 60 day dispensing and perfect adherence.</p> <p>Disease management costs by KDIGO health state were based on MBS fees and resource use estimates from the Deloitte Access Economics 2023 report on the costs of CKD in Australia, plus assumptions regarding additional resources required for patients with more severe kidney disease, and additional specialist visits for all health states.</p> <p>Costs associated with dialysis and transplant were based on the Deloitte Access Economics 2023 report on the costs of CKD in Australia. The calculation of annual dialysis costs assumed that initial access costs would apply to patients initiating and continuing haemodialysis or peritoneal dialysis. The 2021 costs were inflated to 2022 prices using the CPI for medical and hospital services (based on the inflation factor for 2019 to 2022).</p> <p>The costs of acute kidney injury, cardiovascular hospitalisations, amputation adverse events and complications associated with dialysis were based on the weighted average cost of relevant AR-DRGs (v10.0, Round 24, 2019-20), inflated from 2019 to 2022 prices using the CPI for medical and hospital services.</p>

Source: Section 3.2.4, pp269-275 of the submission

Abbreviations: Abbreviations: ABS, Australian Bureau of Statistics; ACE inhibitor, angiotensin-converting enzyme inhibitor; AIHW, Australian Institute of Health and Welfare; ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; ARB, angiotensin II receptor blocker; BMI, body mass index; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HbA1c, glycated haemoglobin; HDL, high density lipoprotein cholesterol; KDIGO, Kidney Disease Improving Global Outcomes; RRT, renal replacement therapy; SBP, systolic blood pressure; TC, total cholesterol; UACR, urine albumin-creatinine ratio; UKPDS, United Kingdom Prospective Diabetes Study

6.62 Figure 3 provides an overview of the model structure.

Figure 3: Model structure overview



Source: Figure 3.3, p265 of the submission

- 6.63 A set of baseline characteristics (demographics, biomarkers, history of complications) is individually generated for each modelled patient.
- 6.64 Patients begin the model in one of 12 KDIGO health states (G2A1 to G4A3) based on their baseline eGFR and UACR; and move to another health state when their modelled eGFR and/or UACR reaches the threshold for a different KDIGO health state.
- 6.65 Patients enter the ESKD module when their eGFR reaches less than 15 mL/min/1.73 m<sup>2</sup>, and are at risk of renal replacement therapy (haemodialysis, peritoneal dialysis, kidney transplant), complications from dialysis, and death from dialysis and transplant states. Patients may transition between dialysis modalities, from dialysis to kidney transplant, and from kidney transplant to dialysis following kidney transplant failure. Following a successful kidney transplant, patients move to the KDIGO G3aA1 health state and follow the same trajectory as patients without a kidney transplant. Patients with ESKD not receiving renal replacement therapy are treated with conservative care and may transition to renal replacement therapy, die from non-cardiovascular, non-renal mortality, or die if their eGFR reaches 3 mL/min/1.73 m<sup>2</sup> or lower.
- 6.66 During each cycle, patients are at risk of diabetes, hypertension, cardiovascular events (myocardial infarction, stroke, unstable angina, transient ischaemic attack), peripheral artery disease, heart failure, acute kidney injury and amputation adverse events. Patients may also die from cardiovascular causes or non-cardiorenal causes.
- 6.67 The model was associated with considerable additional complexity compared to other economic models in chronic kidney disease. In particular, the modelling of cardiovascular complications was a primary source of complexity in the model, yet only represented a small proportion of the incremental differences between treatment arms. The complexity of the model reduces the transparency of the analysis

(with multiple interactions between components) and increases the potential for calculation errors. Many of the components of the model were poorly documented and inadequately justified in the submission.

- 6.68 Despite the substantial complexity involved in capturing individual patient variation in the model, there was very limited variation captured regarding the core mechanic of eGFR/UACR progression; with fixed baseline values based on KDIGO category and fixed changes in eGFR over time. Overall, the modelling of eGFR/UACR progression was poorly justified in the submission.
- 6.69 There were multiple issues identified with the model that are likely to be key drivers, but could not be adequately assessed through sensitivity analyses:
- The modelled overall and incremental populations are not representative of the target incremental population (patients who are not covered under existing SGLT2 inhibitor PBS listings for chronic kidney disease, diabetes and heart failure).
  - The modelled changes in eGFR and UACR over time did not account for individual patient variation and known correlations with each other and patient age.
  - There was no assessment of the impact of variance on treatment effect estimates for eGFR decline and UACR change, or of modelling treatment effects across all KDIGO categories when the available data generally support reductions in eGFR decline for patients with UACR >300 mg/g only.
  - Treatment effects for the modelled incremental population were based on the overall EMPA-KIDNEY population. The impact of modelling outcomes based on the EMPA-KIDNEY incremental population was not assessed. Results for annual eGFR change suggest a smaller treatment effect for the incremental population than for the overall population.
  - The model extrapolated long-term treatment effects from the EMPA-KIDNEY trial (mean follow-up 23.9 months) while patients remain on therapy without accounting for the natural history of chronic kidney disease. Additionally, the model assumed that patients who discontinue empagliflozin or placebo therapy would also stop their background ACE inhibitor/ARB treatment, which was used to justify alternative transition probabilities after treatment discontinuation. This assumption was not reasonable and the alternative transition probabilities are not representative of patients 'off treatment'.
- 6.70 The incremental difference in costs for health care resource items used in the economic evaluation is summarised in Table 12 below.

**Table 12: Disaggregated summary of cost impacts in the economic evaluation (discounted)**

Resource item	Empagliflozin+SC	Placebo+SC	Incremental cost	% incremental
Empagliflozin and standard care		\$607		-14.16%
Disease management	\$6,847	\$6,257	\$590	-2.28%
ESKD conservative therapy	\$279	\$324	-\$44	0.17%
Renal replacement therapy	\$55,479	\$86,348	-\$30,870	119.29%
- dialysis	\$50,514	\$78,476	-\$27,962	108.05%
- dialysis complications	\$2,275	\$3,440	-\$1,165	4.50%
- transplant (initial)	\$2,690	\$4,432	-\$1,742	6.73%
- transplant (ongoing)	\$0	\$0	\$0	0%
Cardiovascular disease	\$5,383	\$5,261	\$123	-0.47%
Acute kidney injury	\$3,687	\$3,791	-\$105	0.40%
Adverse events	\$1,076	\$314	\$763	-2.95%
<b>Total costs</b>		<b>\$102,902</b>		<b>100%</b>

Source: Table 3.58, p332 of the submission; 'Att\_12\_empagliflozin (Jardiance) CKD CEA' model spreadsheet provided with the submission  
Abbreviations: ESKD, end stage kidney disease; SC, standard care

Note: The estimates in the submission were based on the assumption of 60 day dispensing for empagliflozin, which were not corrected during the evaluation.

- 6.71 The difference in cost between treatment arms was driven by the cost offsets associated with lower kidney replacement therapy costs (predominantly dialysis costs) in the empagliflozin plus standard care arm, which far exceeded the additional costs associated with empagliflozin treatment.
- 6.72 The incremental difference in health outcomes estimated in the economic evaluation is summarised in Table 13 below.

Table 13: Disaggregated summary of health outcomes included in the economic evaluation

Health outcome	Empagliflozin+SC	Placebo+SC	Incremental outcome	% incremental
<b>Proportion of patients with events</b>				
ESKD	56.3%	69.7%	-13.4%	-
Peritoneal dialysis	20.9%	27.2%	-6.3%	-
Haemodialysis	40.9%	53.8%	-12.9%	-
Kidney transplant	8.5%	13.2%	-4.7%	-
Renal death	22.0%	29.7%	-7.7%	-
Cardiovascular death	39.9%	40.5%	-0.6%	-
Non-cardiovascular/non-renal death	17.8%	14.0%	3.8%	-
<b>Time in health state (undiscounted)</b>				
<b>By eGFR category<sup>a</sup></b>				
- G2: eGFR 60 to <90 mL/min/1.73 m <sup>2</sup>	0.2760*	0.2350	0.0410*	3.31%*
- G3a: eGFR 45 to <60 mL/min/1.73 m <sup>2</sup>	1.0800*	1.1815	-0.1015*	-8.18%*
- G3b: eGFR 30 to <45 mL/min/1.73 m <sup>2</sup>	2.8410*	2.3385	0.5025*	40.51%*
- G4: eGFR 15 to <30 mL/min/1.73 m <sup>2</sup>	5.2820*	3.7040	1.5780*	127.21%*
- G5: eGFR <15 mL/min/1.73 m <sup>2</sup>	2.1565*	2.9360	-0.7795*	-62.84%*
<b>By UACR category<sup>b</sup></b>				
- A1: UACR <30 mg/g	0.7315*	0.8030	-0.0715*	-5.76%*
- A2: UACR 30-300 mg/g	5.7685*	2.8950	2.8735*	231.64%*
- A3: UACR >300 mg/g	5.1355*	6.6970	-1.5615*	-125.88%*
<b>Total life years (undiscounted)</b>	<b>11.6355</b>	<b>10.3950</b>	<b>1.2405</b>	<b>100%</b>
<b>Total life years (discounted)</b>	<b>8.5096</b>	<b>7.7753</b>	<b>0.7343</b>	<b>-</b>
<b>Health state QALYs (discounted)</b>				
QALYs by KDIGO health states	7.0931	6.4054	0.6877	89.79%
<b>QALY losses (discounted)</b>				
Adverse events	0	0	0	0%
Renal replacement therapy	-0.1413	-0.2197	0.0784	10.24%
CV disease	-0.0587	-0.0580	-0.0007	-0.09%
Acute kidney injury	-0.0153	-0.0157	0.0005	0.06%
<b>Total QALYs (discounted)</b>	<b>6.8779*</b>	<b>6.1120*</b>	<b>0.7659*</b>	<b>100%*</b>

Source: Table 3.59, p332 of the submission; 'Att\_12\_empagliflozin (Jardiance) CKD CEA' model spreadsheet provided with the submission  
Abbreviations: eGFR, estimated glomerular filtration rate; ESKD, end stage kidney disease; QALY, quality adjusted life year; SC, standard care; UACR, urine albumin-creatinine ratio

<sup>a</sup> combines UACR categories

<sup>b</sup> combines eGFR categories

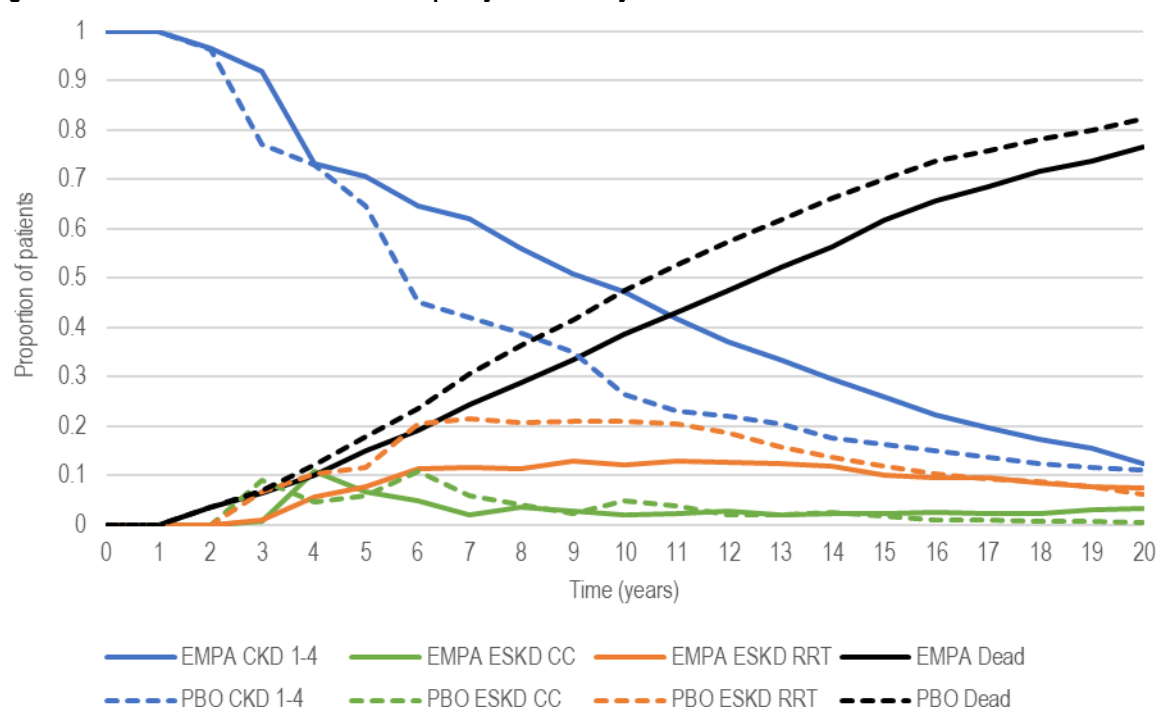
Note: Time in health state and health state QALYs are summarised by eGFR category and UACR category (rather than the 12 included KDIGO categories) and are not mutually exclusive

\* Note that the results presented in Table 13 are derived from post-hoc analyses conducted by the applicant. These analyses were not part of the pre-specified statistical plan for EMPA-KIDNEY. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

- 6.73 The difference in health outcomes between treatment arms was primarily driven by increased survival in patients treated with empagliflozin plus standard care compared to standard care alone (due to a reduction in renal death from ESKD), with patients in the empagliflozin plus standard care arm spending less time in end stage kidney disease (eGFR <15 mL/min/1.73 m<sup>2</sup>) and less time with very severe albuminuria (UACR >300 mg/g).
- 6.74 A comparison of modelled estimates of initiation of renal replacement therapy and all-cause mortality with estimates from the EMPA-KIDNEY trial indicates that modelled estimates may have poor validity. In the model, no patients initiate renal replacement

therapy in the first 2 years, compared with 3.1% of empagliflozin patients and 4.8% of placebo patients in the EMPA-KIDNEY trial. The model generates higher risks of all-cause death at 2 years (6.5% in the empagliflozin arm; 6.9% in the placebo arm) compared to the EMPA-KIDNEY trial (4.3% and 4.9% respectively). The Pre-Sub-Committee Response presented the results of an external validation exercise comparing survival of the Australian cohort of the Study of Heart And Renal Protection (SHARP) extended review with modelled survival (see Figure 2 of the Response) and claimed this demonstrates that the model can be considered externally valid. The ESC considered that uncertainty remained regarding the potential overestimation of survival gains and differences in time to RRT compared to the EMPA-KIDNEY trial, with questionable results in the eGFR progression in the model traces (see Figure 4).

Figure 5: Model traces of health state occupancy over time by treatment arm



Source: Constructed during the evaluation using Att\_12\_empagliflozin (Jardiance) CKD CEA model spreadsheet provided with the submission

Abbreviations: CC, conservative care; CKD, chronic kidney disease stage; EMPA, empagliflozin plus standard care; ESKD, end stage kidney disease; PBO, placebo plus standard care; RRT, renal replacement therapy

6.75 A comparison of modelled outcomes by baseline KDIGO category over 5 years with results from the Chronic Renal Insufficiency Cohort study (Grams 2021) indicated that the modelled estimates for chronic kidney disease progression may have poor validity. The model estimates that no patients in KDIGO categories G2A1 to G4A1 experience ESKD over 5 years, compared with estimates ranging from 0% to 42% of patients from Grams 2021; and the modelled cumulative incidence of ESKD for KDIGO classes G4A2 and G4A3 (56.7% and 89.2%, respectively) exceed the upper 95% confidence limit from Grams 2021 (37% and 74%, respectively).

6.76 The submission presented the results of a stepped economic evaluation, which indicated that the inclusion of the costs of renal replacement therapy and the extrapolation of outcomes to 20 years had the largest impact on the economic evaluation.

6.77 The results of the modelled economic evaluation are presented in Table 14 below.

**Table 14: Results of the economic evaluation**

Component	Empagliflozin+SC	Placebo+SC	Increment
<b>EMPA-KIDNEY modelled overall population (base case)</b>			
Costs		\$102,941	-
QALYs	6.8779*	6.1120	0.7659*
Incremental cost per QALY gained			Empagliflozin dominant
<b>EMPA-KIDNEY modelled incremental population</b>			
Costs		\$83,706	-
QALYs	6.9366 *	6.1269	0.8098*
Incremental cost per QALY gained			Empagliflozin dominant

Source: Table 3.57, p331 and Table 3.61, p335 of the submission

Abbreviations: QALY, quality adjusted life year; SC, standard care

Note: The estimates in the submission were based on the assumption of 60 day dispensing for empagliflozin, which were not corrected during the evaluation.

\* Note that the results presented in Table 14 are derived from post-hoc analyses conducted by the applicant. These analyses were not part of the pre-specified statistical plan for EMPA-KIDNEY. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.78 Based on the modelled economic evaluation, treatment with empagliflozin plus standard care was associated with lower costs and higher QALYs (i.e. was dominant) compared to standard care alone for the treatment of patients with CKD.

6.79 In the model base case, 99.3% of the incremental QALYs, 63.8% of the incremental drug costs and all of the savings associated with ESKD are accrued in the extrapolated period (beyond 2 years).

6.80 For every 1,000 patients treated with empagliflozin plus standard care versus placebo plus standard care and followed up for 20 years, the base case economic evaluation (without discounting) estimated that there would be:

- Additional empagliflozin drug costs of \$ 1 million with additional disease management costs of \$2.4 million (background ACE inhibitor/ARB, CKD health state and adverse event costs); which were offset by decreased costs for dialysis (\$41.7 million) and transplantation (\$2.6 million).
- A decreased incidence of dialysis (139 fewer initiations), transplant (47 fewer transplants), and renal deaths (77 fewer deaths).
- Increased incidence of cardiovascular hospitalisation (51 additional events) but fewer cardiovascular deaths (6 fewer deaths).
- Increased incidence of death due to non-cardiovascular, non-renal causes (38 more deaths).

6.81 The results based on the overall population of the EMPA-KIDNEY trial have limited applicability to the requested incremental population, as a substantial proportion of

patients would be eligible for SGLT2 inhibitor treatment under existing PBS listings for chronic kidney disease, diabetes, and/or heart failure. The modelled population also included a proportion of patients outside of the proposed empagliflozin restriction.

6.82 The results based on the modelled incremental population were not informative of the cost-effectiveness of empagliflozin in the incremental population, due to the following issues:

- As acknowledged in the submission, the modelled incremental population included a proportion of patients from the overlap population (who would meet the dapagliflozin CKD restriction criteria; 13.6%), due to the separate allocation of patients into eGFR and UACR categories rather than allocation based on the observed KDIGO category distribution from the trial, and the use of fixed mean baseline UACR and eGFR values for each KDIGO category from the overall population rather than the incremental population.
- The modelled incremental population included a large proportion of patients with diabetes (50.5%) and heart failure (12.5%), as well as patients outside of the proposed empagliflozin restriction (10.2%).
- The patients who meet the incremental population criteria are from only 2 of the 4 component subgroups (eGFR 25 to <45 mL/min/1.73 m<sup>2</sup> and UACR <200 mg/g; eGFR 20 to <25 mL/min/1.73 m<sup>2</sup> regardless of UACR), with no patients included from the other component subgroups of the incremental population (eGFR >75 to <90 mL/min/1.73 m<sup>2</sup> and UACR ≥200 mg/g; eGFR 25 to 75 mL/min/1.73 m<sup>2</sup> and UACR >5000 mg/g).
- The analysis was based on the treatment effects of empagliflozin in the overall population. Results for annual eGFR change suggest a treatment effect interaction between the overlap and incremental populations, with smaller treatment effects observed in incremental population.

6.83 Limited sensitivity analyses were presented in the submission. The sensitivity analyses were considered largely uninformative as they did not adequately assess the robustness of the modelled economic evaluation due to the issues outlined in paragraph 6.69.

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

### ***Drug cost/patient/year***

6.84 A comparison of empagliflozin use between the trial setting, economic model and budget impact model is presented in Table 15. The estimates in the submission assumed 60 day dispensing for empagliflozin. Given empagliflozin for CKD is not an eligible stage one medicine for 60 day dispensing, the DPMQ was corrected during the evaluation (\$61.01) to reflect a maximum quality of 1 pack (30 tablets) dispensed, updated for current mark-ups at 1 July 2023.

**Table 15: Drug cost per patient per year for empagliflozin**

	EMPA-KIDNEY trial	Economic model	Financial estimates
Daily dose	10 mg daily	10 mg daily	10 mg daily
Cost per pack of 30 tablets (proposed DPMQ) <sup>a</sup>	-	\$61.01	\$61.01
Adherence		100%	90%
No. scripts per year	-	12.1750 (=365.25 ÷ 30 × 100%)	10.9575 (=365.25 ÷ 30 × 90%)
Cost per year	-	\$742.80 <sup>b</sup>	\$668.52 <sup>c</sup>
Proportion of patients on treatment (persistence)	After a mean follow-up of 23.9 months, 74.3% of patients in the empagliflozin arm remained on treatment	Year 1: 88.3% Year 2: 78.6% Year 3: 69.7% Year 4: 61.3% Year 5: 51.9% Year 6: 43.9%	100%

Source: Table 1.5.14.1.1, p924 of Attachment 16 R1849 HTA analysis; Attachment 12 empagliflozin (Jardiance) CKD CEA economic model; and Attachment 20 empagliflozin (Jardiance) CKD UCM financial implications spreadsheet provided with submission

Abbreviations: DPMQ, dispensed price for maximum quantity

<sup>a</sup> The DPMQ was revised during the evaluation to reflect 30 day dispensing and July 2023 fees and mark-ups. The submission's DPMQ was based on the assumption that 60 day dispensing would apply to empagliflozin for CKD.

<sup>b</sup> The submission's estimated cost per year for the economic model was \$658.55, based on 60 day dispensing, a DPMQ of \$108.18 and 6.0875 (=365.25/60) scripts per year.

<sup>c</sup> The submission's estimated cost per year for the financial implications was \$592.69, based on 60 day dispensing, a DPMQ of \$108.18 and 5.47875 (=365.25/60×90%) scripts per year.

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

- 6.85 This submission was considered by DUSC.
- 6.86 The submission used an epidemiological approach to estimate the utilisation and financial impacts associated with a PBS listing of empagliflozin for the treatment of CKD. The submission's estimates were based on two subpopulations: those eligible under the existing PBS listing for dapagliflozin (overlap subgroup) and an incremental subgroup of patients who are not currently eligible to receive dapagliflozin on the PBS (incremental subgroup).
- 6.87 For the incremental subgroup, empagliflozin was positioned as an add-on to standard care which includes an ACE inhibitor or ARB. For the overlap subgroup, empagliflozin (added to standard care) was positioned as a substitute for patients who would be eligible to receive PBS-listed dapagliflozin (added to standard care) for CKD. However, the submission stated that substitution for dapagliflozin was not captured in the utilisation and financial estimates, arguing this was a conservative approach as any savings from switching would not be captured as a cost offset against the cost of empagliflozin. Estimates also include the cost of dapagliflozin in patients who would not switch to empagliflozin. The submission also noted that the uptake rates (and costs) for the overlap subgroup represent the total SGLT2 inhibitor class (i.e. would include use of both empagliflozin and dapagliflozin in practice).
- 6.88 The estimation of eligible patients for both population subgroups used the same parameters (apart from estimates of the proportion of patients within the different eGFR and UACR categories).

6.89 Key inputs used to derive the financial estimates are presented in Table 16.

**Table 16: Data sources and parameter values applied in the utilisation and financial estimates**

Data	Value	Source	Commentary on the submission	DUSC comments
<b>Eligible population</b>				
Australian population 18+ years	2024: 21,411,852 2025: 21,744,502 2026: 22,073,220 2027: 22,393,101 2028: 22,714,178 2029: 23,030,499	ABS population projections, Series B (ABS 3222.0)		
% Australian adults with CKD	11%	AIHW 'Chronic Kidney Disease: Australian facts', updated 23 August 2022. The source was the same as in the July 2021 dapagliflozin submission (measured eGFR and urine albumin-creatinine ratio (UACR) results from the 2011-2012 National Health Measures survey, NHMS), but the estimate used was different. The dapagliflozin submission used 10% (total proportion of adults with biomarkers indicating chronic kidney disease). The submission used a more recent AIHW analysis of these data with prevalence specified as 11% rather than 10%. The AIHW analysis noted that participants with missing or unreliable measurement of eGFR or UACR were excluded from the denominator population, and as a result, numbers may differ from numbers published in other sources. A sensitivity analysis was also presented using the original 10% estimate.	The submission noted that the assumed prevalence of 10% was considered reasonable by PBAC (Table 23, Dapagliflozin PSD, November 2021 PBAC meeting).	DUSC considered that there was significant uncertainty in the current prevalence of CKD in the Australian population.  DUSC noted that, based on a single biological marker, 1 in 3 adults are at risk of developing CKD, 1 in 10 have early signs of CKD, and 1.7 million may have undiagnosed CKD.
Adults likely to be diagnosed with CKD	Yr 1: 60% Yr 2: 65% Yr 3: 70% Yr 4: 75% Yr 5: 80% Yr 6: 85%	PBAC suggested that the diagnosis rate should be 50% in year 1 (2022) of dapagliflozin estimates, increasing by 5% per year (para 15.4, Dapagliflozin PSD, November 2021 PBAC meeting, meaning diagnosis rate would be 60% in year 1 (2024) of empagliflozin estimates.	It is unclear whether the diagnosis rate will continue to increase in a linear fashion.	DUSC considered that the estimated proportion of adults diagnosed with CKD to be an overestimate and that it was unclear whether the rate of diagnosis would continue to increase in a linear fashion.

Public Summary Document - November 2023 PBAC Meeting

Data	Value	Source	Commentary on the submission	DUSC comments
% Overlap subgroup	7.5%	As estimated by PBAC in consideration of dapagliflozin for CKD (Table 23, Dapagliflozin PSD, November 2021 PBAC Meeting). PBAC considered that 7.5% of the diagnosed population would be eligible based on the UACR criterion in the dapagliflozin restriction and 33% would be eligible based on the eGFR criterion. As the UACR criterion is the more restrictive, this parameter was estimated at 7.5%.	This was reasonable.	DUSC considered that the patient population in the overlap subgroup was reasonable.
% Incremental subgroup	8.4%	<p>Proportion of patients with eligible eGFR levels from 2011-2012 NHMS data (same source as for overlap subgroup above). Patients with Stage 5 CKD were excluded (0.8%) based on the number of patients who received renal replacement therapy from the Australian and New Zealand Dialysis and Transplant Registry (ANZDATA) from 2011.</p> <p>Patients with micro- and macroalbuminuria from the same NHMS dataset (of all patients with albuminuria, 88% had microalbuminuria, and 12% had macroalbuminuria), used in the absence of more granular data, assuming that microalbuminuria was a reasonable proxy for patients with UACR between 30 and 200 mg/g, and macroalbuminuria represented patients with UACR &gt;200 mg/g. The submission assumed that patients were uniformly distributed within each eGFR stage.</p> <p>The NHMS data did not report the proportion of patients with UACR &gt;5,000 mg/g, so the submission's base case assumed that no patients would meet this criterion.</p>	<p>It is unclear whether proportions of patients with micro or macroalbuminuria from the NHMS dataset are representative of proportions with micro or macroalbuminuria or normal albumin levels within each eGFR stage. Distribution of albuminuria is likely to be different within more or less severe kidney disease stages.</p> <p>This assumption that no patients met the criterion of UACR &gt;5,000 mg/g may have underestimated the size of the eligible incremental subgroup. The submission's sensitivity analysis included data from Neuen (2023), in which 1,126 patients met the criteria for eGFR ≥25 to 75 and UACR &gt;5,000 mg/g.</p>	DUSC considered that the patient population in the incremental subgroup was uncertain and potentially an underestimate.
Proportion of patients who are stable on angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs)	80%	Suggested by PBAC as an alternative to the dapagliflozin submission's assumption of 100% of patients (para 14.2, Dapagliflozin PSD, November 2021 PBAC meeting).	This was reasonable.	DUSC noted that it is unclear whether this estimate is reflective of the restriction criteria of maximum tolerated dose.

Public Summary Document - November 2023 PBAC Meeting

Data	Value	Source	Commentary on the submission	DUSC comments
% patients without polycystic kidney disease	95.7%	4.3% of patients with CKD were reported to have polycystic kidney disease, based on Queensland registry data (Mallett 2014), the same source used in the dapagliflozin submission (Table 23, Dapagliflozin PSD, November 2021 PBAC meeting). The submission noted that more patients with other renal conditions were excluded from the dapagliflozin estimates (total 5.66%) due to additional renal conditions in the exclusion criteria for the DAPA-CKD trial.	The PBAC previously considered that the applicability of the Queensland data was unknown, and patients with a history of cytotoxic or immunosuppressive therapy for kidney disease, or an organ transplant had not been excluded. However, as the overall impact of further changes was likely to be small, these estimates were reasonable (Table 23, Dapagliflozin PSD, November 2021 PBAC meeting).	DUSC noted that patients with a history of cytotoxic or immunosuppressive therapy for kidney disease, or an organ transplant had not been excluded.

Public Summary Document - November 2023 PBAC Meeting

Data	Value	Source	Commentary on the submission	DUSC comments
% patients without type 2 diabetes	50%	Suggested by PBAC as an alternative estimate (Table 23, Dapagliflozin PSD, November 2021 PBAC meeting). Based on 2019 ANZDATA registry data, in which close to 50% of patients had type 2 diabetes on initiation of renal replacement therapy. PBAC further noted that in the DAPA-CKD trial, 67.6% of patients had type 2 diabetes at baseline (32.4% without type 2 diabetes). Approximately 55% of patients in the EMPA-KIDNEY trial did not have type 2 diabetes. An alternative estimate of 57.4% without type 2 diabetes was derived from an Australian study of patients who would meet the eligibility criteria of the EMPA-KIDNEY trial, presented in the submission as a sensitivity analysis (see Section 4.6).	The 50% estimate was suggested by PBAC in the dapagliflozin November 2021 submission to represent the total proportion of patients who are not eligible for SGLT2 inhibitor treatment for type 2 diabetes (i.e., inclusive of those without type 2 diabetes, <b>and</b> those with type 2 diabetes but with HbA1c $\leq$ 7%). This estimate was proposed by PBAC in November 2021, whereas the current submission's argument	DUSC noted that the estimated proportion of patients without T2DM of 50% suggested by PBAC in the November 2021 public summary document for dapagliflozin was inclusive of those with diabetes with a HbA1C of $\leq$ 7%.
% patients with type 2 diabetes who are not eligible for SGLT2 inhibitors due to HbA1c $\leq$ 7%	27.9%	The submission quoted the July 2021 Dapagliflozin PSD (para 6.61, Dapagliflozin PSD, July 2021 PBAC meeting), stating that the estimate of CKD patients with type 2 diabetes 'did not explicitly account for [SGLT2] eligibility according to existing and proposed PBS restrictions, and argued that in practice, it is likely that not all CKD patients with type 2 diabetes would meet the type 2 diabetes restriction requirements for SGLT2 inhibitors.  The submission therefore estimated the proportion of type 2 diabetes patients not eligible for PBS-listed SGLT2 inhibitor treatment based on a cross-sectional study of patients with type 2 diabetes and cardiovascular disease using the MedicineInsight primary care database (Marson 2021), in which 55.8% of patients had HbA1c of $\leq$ 7%. This proportion was applied to the proportion of CKD patients with type 2 diabetes (55.8% x 50%) to reach the submission's estimate of 27.9% of CKD patients with type 2 diabetes who are not eligible for PBS-listed SGLT2 therapy.	was based on a quote from the July 2021 PBAC meeting.  Adding an additional 27.9% of type 2 diabetes patients may have overestimated the total number of CKD patients who are not eligible for SGLT2 inhibitor therapy for diabetes.	DUSC considered that the proportion of patients with T2DM who are not eligible for SGLT2 inhibitor are already accounted for in the 50% estimate of patients with CKD but without T2DM.

Public Summary Document - November 2023 PBAC Meeting

Data	Value	Source	Commentary on the submission	DUSC comments
% patients with CKD who do not have heart failure	90%	Proportion of patients in EMPA-KIDNEY trial who did not have heart failure, which is consistent with the estimate used in the dapagliflozin submission (Table 23, Dapagliflozin PSD, November 2021 PBAC meeting).	This was appropriate.	DUSC considered this was appropriate.
% patients with kidney failure who do not initiate renal replacement therapy (RRT)	99.2%	Estimated to exclude patients who have progressed to end stage kidney disease. Based on 0.8% of patients who initiated RRT in 2011 (ANZDATA Annual report 2021).	This proportion has not been appropriately applied. Patients with end stage kidney disease have already been excluded from the eligible patient populations based on eGFR criteria. This estimate should have been applied as a proportion of patients discontinuing treatment throughout each year rather than as part of estimating the eligible patient populations.	DUSC noted that these patients are excluded from the eligible population and as the sponsor has used a prevalent pool this has already been accounted for.
<b>Treatment utilisation</b>				
Uptake rate – overlap subgroup	Yr 1: % Yr 2: % Yr 3: % Yr 4: % Yr 5: % Yr 6: %	Sponsor assumption. Represents overall uptake of the SGLT2 inhibitors (i.e. either empagliflozin or dapagliflozin).	Assumed uptake rates are uncertain.	DUSC considered this to be an overestimate.
Uptake rate – incremental subgroup	Yr 1: % Yr 2: % Yr 3: % Yr 4: % Yr 5: % Yr 6: %	Sponsor assumption. The submission assumed a more rapid uptake in the incremental subgroup given the lack of targeted PBS-listed treatment options for these patients.	Assumed uptake rates are uncertain.	DUSC considered this to be an underestimate.

Public Summary Document - November 2023 PBAC Meeting

Data	Value	Source	Commentary on the submission	DUSC comments
Treatment compliance	90%	As proposed for empagliflozin for heart failure in a pre-PBAC response (Table 14, Empagliflozin PSD, November 2022 PBAC meeting), and incorporated into revised financial estimates in a submission considered and recommended by the PBAC in December 2022.	In its consideration of the dapagliflozin CKD submission, the PBAC noted that the DAPA-HF (heart failure) trial adherence was 96.7% but the HFrEF resubmission applied 85% adherence in financial estimates. The PBAC considered there was no reason to expect that adherence for CKD would be higher and recommended that the treatment adherence be reduced to 85% (Table 19, p41, and para 11.8, Dapagliflozin PSD, September 2021 PBAC meeting).	DUSC considered this to be an underestimate, however the estimate was not required for the prevalence-based approach, except that there is a stopping rule (end stage kidney disease/transplant) but this represents only a small proportion and these patients are already excluded from the eligible population.
<b>Costs</b>				
Empagliflozin 30 x 10 mg tablets	\$44.66 (AEMP)	Requested price. The submission's calculated DPMQ was \$108.18 based on 60 day dispensing (calculated as \$109.03 using 1 July 2023 markups).	This was corrected during the evaluation. Based on 30 day dispensing (and 1 July 2023 markups), the DPMQ was \$61.01	
Weighted average patient co-payment	\$12.97	Based on beneficiary distribution for dapagliflozin for treatment of CKD from September 2022 to April 2023 (PBS: 97.93%; RPBS: 2.07%)	This was reasonable.	

Source: Table 4.1.1, Attachment 4, pp199-203 of the commentary.

Abbreviations: ABS, Australian Bureau of Statistics; AEMP, approved ex-manufacturer price; AIHW, Australian Institute of Health and Welfare; CKD, chronic kidney disease; DPMQ, dispensed price for maximum quantity; HFrEF, heart failure with reduced ejection fraction; PSD, Public Summary Document; SGLT2-2, sodium glucose cotransport-2; RRT, renal replacement therapy; UACR, urine albumin-creatinine ratio.

6.90 Table 17 summarises the estimated patients treated, scripts dispensed, and net cost to the PBS/RPBS of listing empagliflozin for the treatment of CKD for the overlap and incremental subgroups and for the total population.

Table 17: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Overlap subgroup<sup>a</sup></b>						
Number of patients treated	1	2	3	3	4	5
Number of scripts dispensed <sup>b</sup>	6	7	8	9	10	11
Cost to PBS/RPBS less co-payments	12	12	13	14	14	15
<b>Incremental subgroup</b>						
Number of patients treated	2	16	3	4	5	17
Number of scripts dispensed <sup>b</sup>	7	8	9	10	11	18
Cost to PBS/RPBS less co-payments	12	13	13	14	14	15
<b>Total</b>						
Number of patients treated	4	17	19	19	19	19
Number of scripts dispensed <sup>b</sup>	10	18	20	20	20	20
<b>Total cost to PBS/RPBS less co-payments</b>	13	15	21	22	23	24

Source: Table 4.16, p362; Table 4.17, p363; Table 4.19, p364 of the submission.

<sup>a</sup> The submission did not estimate the extent of use and expected change in the use of dapagliflozin, associated with the proposed PBS listing of empagliflozin. Estimates for the overlap subgroup represent the total SGLT2 inhibitor class (i.e. would include use of both empagliflozin and dapagliflozin in practice).

<sup>b</sup> Assuming 10.96 scripts per year (12.18 scripts/year with assumed adherence of 90%).

Note: The number of scripts per year and total cost was changed during the evaluation to correspond to current 30 day dispensing, and the total cost was based on a DPMQ of \$61.01 incorporating markups at 1 July 2023

The redacted values correspond to the following ranges:

- 1 20,000 to < 30,000
- 2 30,000 to < 40,000
- 3 50,000 to < 60,000
- 4 60,000 to < 70,000
- 5 70,000 to < 80,000
- 6 300,000 to < 400,000
- 7 400,000 to < 500,000
- 8 500,000 to < 600,000
- 9 600,000 to < 700,000
- 10 700,000 to < 800,000
- 11 800,000 to < 900,000
- 12 \$10 million to < \$20 million
- 13 \$20 million to < \$30 million
- 14 \$30 million to < \$40 million
- 15 \$40 million to < \$50 million
- 16 40,000 to < 50,000
- 17 80,000 to < 90,000
- 18 900,000 to < 1,000,000
- 19 100,000 to < 200,000
- 20 1,000,000 to < 2,000,000
- 21 \$50 million to < \$60 million
- 22 \$60 million to < \$70 million
- 23 \$70 million to < \$80 million
- 24 \$80 million to < \$90 million

6.91 The estimated net cost to the PBS/RPBS (based on 30 day dispensing and 1 July 2023 markups) for the overlap subgroup was \$10 million to < \$20 million in Year 1, increasing to \$40 million to < \$50 million in Year 6, an estimated cumulative net cost of \$100 million to < \$200 million in the first six years of listing. The estimated net cost to the PBS/RPBS represents the total SGLT2 inhibitor utilisation in the overlap subgroup.

- 6.92 The submission estimated that the incremental subgroup will be larger than the CKD population currently eligible for dapagliflozin. The estimated net cost to the PBS/RPBS (based on 30 day dispensing and 1 July 2023 markups) for the incremental subgroup was \$10 million to < \$20 million in Year 1, increasing to \$40 million to < \$50 million in Year 6, an estimated cumulative net cost of \$100 million to < \$200 million in the first six years of listing.
- 6.93 The total estimated net cost to the PBS/RPBS for both populations was \$30 million to < \$40 million in Year 1, increasing to \$80 million to < \$90 million in Year 6, an estimated cumulative net cost of \$300 million to < \$400 million.
- 6.94 The estimated utilisation and net cost of listing empagliflozin for CKD on the PBS were uncertain for the following reasons:
- The estimated utilisation of empagliflozin in the overlap subgroup did not incorporate offsets associated with use/substitution of dapagliflozin and only provides an estimate of use and costs of SGLT2 inhibitors as a whole.
  - The inclusion of an additional proportion of patients ineligible for SGLT2 inhibitor therapy for type 2 diabetes to the PBAC's previous estimates may have overestimated the total number of CKD patients who are not eligible for SGLT2 inhibitor therapy for diabetes (and who would therefore be eligible under the requested CKD restriction).
  - DUSC considered that there was significant uncertainty in the current prevalence of CKD in the Australian population. DUSC noted that based on a single biological marker, 1 in 3 adults are at risk of developing CKD, 1 in 10 have early signs of CKD, and 1.7 million may have undiagnosed CKD.
  - DUSC considered that the estimated proportion of adults diagnosed with CKD to be an overestimate and that it was unclear whether the rate of diagnosis would continue to increase in a linear fashion.
  - In estimating eligible patients in the incremental subgroup, it is unclear whether proportions of patients with different albuminuria levels from the National Health Measures Survey dataset are representative of the distribution of albuminuria levels within each eGFR stage. Distribution of albuminuria is likely to be different within more or less severe eGFR stages.
  - DUSC noted that the estimated proportion of patients without type 2 diabetes mellitus (T2DM) of 50% represented the total proportion of patients (inclusive of those with HbA1c  $\leq 7\%$ ) who are not eligible for sodium-glucose co-transporter 2 (SGLT2) inhibitors treatment for T2DM. As a result, DUSC considered that the proportion of patients with T2DM who are not eligible would, in effect, be an overestimate.
  - DUSC considered that the proportion of patients with kidney failure who do not initiate renal replacement therapy (RRT) to be inaccurate due to double counting

of those patients who have progressed to end stage kidney disease. However, DUSC considered the effect on the estimates to be small.

- DUSC considered that the uptake rates for the overlap subgroup to be overestimated as it does not account for the current dapagliflozin treated population and assumes that the dapagliflozin market is not already saturated. DUSC considered that the uptake rate assumption for the incremental subgroups to be an underestimate as it assumes only a slightly higher uptake in a patient group where no other targeted treatment is currently available. .
- DUSC considered that the overall usage is difficult to estimate due to confounding effects when the treatment can also be indicated for conditions which often coincide in patients with CKD such as T2DM and heart failure.

6.95 The ESC was concerned that the cost effectiveness of the lowest risk incremental subgroup (eGFR >75 and <90mL/min/1.73m<sup>2</sup> and UACR ≥200mg/g) was not established in the cost utility analysis and empagliflozin may be less effective in this subgroup. The inclusion of this group in the financial estimates adds to uncertainty, as the size of this subgroup population may influence the overall cost-effectiveness of the population.

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

### **Quality Use of Medicines**

- 6.96 The sponsor proposed awareness and educational activities to address the need for clinician education and support for peri-procedural practice and ketoacidosis, candidiasis and urinary symptoms previously noted by DUSC (6.75, Dapagliflozin PSD, July 2021 PBAC meeting). In addition, the sponsor proposed ongoing engagement and communication with pharmacists to ensure there is no inadvertent co-prescribing of empagliflozin for other indications such as type 2 diabetes and heart failure, as well as concomitant use with other SGLT2 inhibitors. The submission noted that the brand name and trade pack for empagliflozin will be the same across all indications to minimise the risk of patient confusion. DUSC considered that there are potential age-related effects in patients with co-morbidities and with potential co-prescribing of empagliflozin (and/or other SGLT2 Inhibitors) in patients with T2DM and heart failure.
- 6.97 The submission noted that the differences in renal dosing recommendations may present some confusion for healthcare professionals, and proposed continued educational support to ensure healthcare professionals understand the contraindications regarding eGFR levels and follow guidance in the Product Information for empagliflozin (once TGA-approved). DUSC considered that the complexity of empagliflozin's restriction criteria and the differences it has with dapagliflozin may cause difficulties for prescribers in practice.

## **Financial Management – Risk Sharing Arrangements**

- 6.98 The submission did not propose a Risk Sharing Arrangement. A Risk Sharing Arrangement is currently in place for empagliflozin for heart failure. The PBAC recommended Risk Sharing Arrangements for dapagliflozin (6.4, Dapagliflozin PSD, March 2022 PBAC meeting) and for finerenone (7.10, Finerenone PSD, March 2023 PBAC meeting) for their CKD listings. The ESC advised that it would be appropriate for the overlap population to be added to the current dapagliflozin Risk Share Arrangement for CKD and for the incremental population to be also added with an appropriate increase in the cap to accommodate the increased population.
- 6.99 The Pre-PBAC response indicated that the sponsor agreed to join the current Risk Share Arrangement for the overlap population at no increased cost to the Australian Government.

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

## **7 PBAC Outcome**

### **Empagliflozin - cost-minimisation approach versus dapagliflozin (overlap population)**

- 7.1 The PBAC recommended extending the listing of empagliflozin, on the basis that it should be available as a General Schedule Authority Required (STREAMLINED) listing for the treatment of chronic kidney disease (CKD), as an add-on to standard care, for patients with an eGFR of  $\geq 25$  to  $\leq 75$  mL/min/1.73 m<sup>2</sup> and a UACR of  $\geq 200$  to  $\leq 5,000$  mg/g. The PBAC's recommendation for listing was based on its assessment that the cost-effectiveness of empagliflozin would be acceptable if it were cost-minimised against dapagliflozin.
- 7.2 The PBAC considered that the equi-effective doses were empagliflozin 10 mg once per day and dapagliflozin 10 mg once per day.
- 7.3 The PBAC noted the consumer comments from individuals and organisations were generally supportive of an additional SGLT2 inhibitor being available on the PBS for treatment to slow progression of CKD.
- 7.4 The PBAC accepted dapagliflozin (add-on to standard care) as the appropriate comparator for the overlap population i.e. patients enrolled in the EMPA-KIDNEY trial who would be eligible for PBS subsidised treatment with dapagliflozin for CKD, based on baseline eGFR and UACR.
- 7.5 The PBAC noted the primary clinical evidence supporting empagliflozin in the proposed populations was the EMPA-KIDNEY trial. The trial demonstrated that empagliflozin when added to standard care provided an improvement in efficacy over standard care alone based on the primary composite outcome (time to first CKD progression or cardiovascular death, HR 0.72 95% CI 0.64, 0.82), over a median duration of follow-up of 24.33 months. The PBAC also noted the statistically significant improvement in the secondary composite outcome of time to first adjudicated

- cardiovascular death or Stage 5 CKD compared to placebo plus standard care (HR 0.73, 95% CI 0.59, 0.89).
- 7.6 For the comparison with dapagliflozin in the overlap population, the PBAC noted the submission relied on an indirect comparison of empagliflozin (EMPA-KIDNEY) to dapagliflozin (DAPA-CKD), with placebo as the common reference. Analyses included indirect comparisons using the EMPA-KIDNEY overall population and *post hoc* subgroup analyses of the EMPA-KIDNEY overlap population.
- 7.7 The results of the ITC showed no statistically significant difference between treatment with empagliflozin compared to dapagliflozin for the primary composite outcome; however, all the results, as presented in Table 8, numerically favoured dapagliflozin. The PBAC considered the treatment effects of empagliflozin were likely non-inferior to those for dapagliflozin given no statistically significant differences in the results of the ITC, the class effect of SGLT2 inhibitors having been confirmed in other indications, and the recent meta-analysis presented in Nuffield et al. 2022 (see paragraph 4.11).
- 7.8 The PBAC noted the difficulty in interpreting the indirect comparison of safety outcomes as highlighted in paragraph 6.40. However, the PBAC considered that for the comparison with dapagliflozin, in the overlap population, the claim of non-inferior comparative safety was reasonable given this would be consistent with substantial experience with this class of medicine in clinical practice (see paragraph 6.42).
- 7.9 The PBAC noted the cost-minimisation approach (CMA) for empagliflozin versus dapagliflozin in adult CKD patients with eGFR 25 to 75 mL/min/1.73 m<sup>2</sup> and UACR 200 to 5,000 mg/g. The PBAC considered this approach was reasonable based on equi-effective doses of empagliflozin 10 mg once daily and dapagliflozin 10 mg once daily, without the inclusion of any differences in GP visits and no application of 60 day dispensing in the price calculations.
- 7.10 The PBAC noted the uptake of empagliflozin in the overlap population was uncertain, and that the estimated usage and financial implications provided in the submission covered the entire SGLT2 inhibitor class. The PBAC considered it was appropriate for the current Risk Sharing Arrangement (RSA) for dapagliflozin in this indication to form the basis of the estimates for this class of medicine, and that empagliflozin would need to join the current RSA with no increase to the caps. The PBAC noted that the pre-PBAC response indicated the sponsor agreed to join the current RSA for the overlap population at no increased cost to the Australian Government.
- 7.11 The PBAC considered that the clinical data supported PBS listing for empagliflozin that aligns with the CKD listing for dapagliflozin (finalised PBS restriction wording shown in Section 8 below). The PBAC noted the pre-PBAC response indicated the sponsor would accept the same restriction wording as the current dapagliflozin CKD listing.
- 7.12 The PBAC advised that empagliflozin is suitable for prescribing by nurse practitioners for continuing therapy only. This would be consistent with recommended arrangements for dapagliflozin for CKD.

- 7.13 The PBAC recommended that the Early Supply Rule should apply, which would be consistent with the recommended arrangements for dapagliflozin for CKD.
- 7.14 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because empagliflozin is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over dapagliflozin, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.
- 7.15 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

**Empagliflozin – cost-effectiveness analysis versus placebo (incremental population)**

- 7.16 The PBAC did not recommend the listing of empagliflozin for the proposed incremental CKD population which was based upon the *post hoc* sub-group analysis in the EMPA-KIDNEY trial which showed little or no improvement from empagliflozin in patients categorised as low, moderate and high risk (KDIGO staging) or in those patients with UACR < 200mg/g at baseline. The PBAC did not consider the *post hoc* subgroup analyses of the EMPA-KIDNEY trial adequately demonstrated a benefit in the broadened indication for CKD. The PBAC noted the modelled treatment effects were not representative of the incremental population, and the overall complexity and uncertainty of the cost-effectiveness analysis made it uninformative.
- 7.17 The PBAC considered the primary reason for this outcome was due to the comparative clinical evidence provided.
- 7.18 The PBAC noted the consumer comments from organisations supporting use of empagliflozin in a broader population versus that PBS subsidised for dapagliflozin. The PBAC acknowledged the need for effective therapy in CKD for patients at high risk of disease progression.
- 7.19 The PBAC accepted placebo (add-on to standard care) as the appropriate comparator for the incremental population (i.e. patients enrolled in the EMPA-KIDNEY trial who would **not** be eligible for PBS subsidised treatment with dapagliflozin for CKD, based on baseline eGFR and UACR).
- 7.20 The PBAC considered the various subgroup analyses of the EMPA-KIDNEY trial provided confirmation of KDIGO staging (based on UACR and eGFR) to predict prognosis. The PBAC noted pre-specified subgroup analyses for the primary composite outcome of CKD progression or cardiovascular death in the EMPA-KIDNEY trial showed significant treatment effect interaction by baseline diabetes status (p=0.0598) and

albuminuria subgroups (UACR<30, 30-300, and >300 mg/g; p=0.0174), with a trend of decreasing treatment effect in patients without diabetes or with a lower baseline UACR (UACR ≤300 mg/g) (see paragraph 6.24). The PBAC considered KDIGO staging is probably both a quantitative and qualitative treatment effect modifier with empagliflozin resulting in little or no improvement in patients categorised as low, moderate and high risk (see Table 7 and paragraph 6.27). Specifically, the PBAC considered empagliflozin likely resulted in little or no improvement in patients with CKD outside the range of UACR specified in the dapagliflozin restriction.

- 7.21 Overall, the PBAC did not consider the submission adequately demonstrated a benefit in the incremental population.
- 7.22 The PBAC did not find the economic model informative to support a listing for the incremental population. The PBAC noted the ESC and the evaluation raised several issues with regards to the economic model (see issues summarised in paragraphs 6.69 and 6.82). The PBAC specifically noted the following issues:
- Modelled treatment effects were not representative of the incremental population as the analysis was based on the treatment effects of empagliflozin in the overall population
  - Modelled changes in eGFR and UACR did not account for within patient variation and collinearity
  - The analysis assumed prognosis/transition probabilities based on the overall trial population
  - Extrapolated treatment effects did not account for the natural history of CKD
  - The model assumed patients who discontinue empagliflozin or placebo therapy would also stop their background ACE inhibitor/ARB treatment, which was used to justify alternative transition probabilities after treatment discontinuation.
  - Sensitivity analyses were largely uninformative as they did not assess the robustness of the modelled economic evaluation due to the issues outlined in paragraph 6.69.
- 7.23 The PBAC noted DUSC's advice that the financial estimates are highly sensitive to the projected size of the incremental population as it consists of a broad range of sub populations. The PBAC further noted DUSC's consideration that the treatment uptake rate for the incremental group was likely underestimated as no other subsidised targeted treatment was available for this group.
- 7.24 The PBAC considered any resubmission for empagliflozin for a broader population should reconsider which subgroups are nominated and ensure they include significantly high UACR. The economic issues raised in paragraphs 6.69, 6.82 and 7.22 and utilisation and financial issues raised in paragraphs 6.94 and 7.23 would also need to be addressed.

7.25 The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.

**Outcome:**

Not recommended

## 8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No.of Rpts	Available brands
EMPAGLIFLOZIN					
empagliflozin 10 mg tablet, 30	NEW MP NP	1	30	5	Jardiance
<b>Restriction Summary: 13230 / Treatment of Concept: 13230 :</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) – [New 2]					
Prescribing rule level	<b>Administrative Advice:</b> <b>Continuing Therapy Only:</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>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.				
	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.				
<b>Indication:</b> Chronic kidney disease					
<b>Clinical criteria:</b>					
Patient must have a diagnosis of chronic 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 have an estimated glomerular filtration rate of between 25 to 75 mL/min/1.73 m <sup>2</sup> inclusive prior to initiating treatment with this drug,					
<b>AND</b>					
<b>Clinical criteria:</b>					
Patient must have a urinary albumin to creatinine ratio of between 200 to 5000 mg/g (22.6-565 mg/mmol) inclusive 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 not be receiving treatment with another sodium-glucose co-transporter 2 (SGLT2) inhibitor,					
<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>Prescribing Instructions:</b> Patients with polycystic kidney disease, lupus nephritis or ANCA-associated vasculitis; patients requiring or with a recent history of cytotoxic or immunosuppressive therapy for kidney disease; and patients with an organ transplant are not eligible for treatment with this drug.

***These restrictions 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**

The sponsor had no comment.