7.02 EMPAGLIFLOZIN, Tablet 10 mg, Jardiance®, Boehringer Ingelheim Pty Ltd.

1 Purpose of submission

1.1 The Standard Re-entry resubmission requested an extension of the current empagliflozin Authority Required (STREAMLINED) listing to include the incremental population that was not recommended by the PBAC at the November 2023 meeting. The incremental population includes 4 distinct subgroups of patients with:

- eGFR 20 to <25 mL/min/1.73 m^2 regardless of UACR.
- eGFR 25 to <45 mL/min/1.73 m^2 with UACR <200 mg/g.
- eGFR 25 to 75 mL/min/1.73 m^2 with UACR >5,000 mg/g.
- eGFR >75 to 90 mL/min/1.73 m^2 with UACR ≥200 mg/g.

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus standard care.

Table 1: Key components of the clinical issue addressed in the resubmission (as stated in the resubmission)

Component	Description
Population	CKD patients with: - eGFR 20 to <25 mL/min/1.73 m^2 regardless of UACR. - eGFR 25 to <45 mL/min/1.73 m^2 and UACR <200 mg/g. - eGFR 25 to 75 mL/min/1.73 m^2 and UACR >5,000 mg/g. - eGFR >75 to 90 mL/min/1.73 m^2 and UACR ≥200 mg/g.
Intervention	Empagliflozin 10 mg once daily, add-on to standard care.
Comparator	Placebo, add-on to standard care. Standard care includes treatment with an ACE inhibitor or ARB to reduce proteinuria and reduce cardiovascular risk.
Outcomes	Composite of kidney disease progression and cardiovascular death, all-cause mortality, hospitalisation for heart failure, all-cause hospitalisations, kidney disease progression, cardiovascular death, composite of cardiovascular death and ESKD, annual rate of change in eGFR, and EQ-5D-5L.
Clinical claim	Empagliflozin plus standard care is superior in terms of efficacy and non-inferior in terms of safety compared to placebo plus standard care.

Source: Table 1.2, p21 of the resubmission.
Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; UACR, urinary albumin to creatinine ratio.
Note: The proposed expanded population is CKD patients with eGFR 20 to 90 mL/min/1.73 m^2; with patients with eGFR 45 to 90 mL/min/1.73 m^2 requiring a UACR ≥200 mg/g. This includes the currently listed CKD population (eGFR 25 to 75 mL/min/1.73 m^2 and UACR 200 to 5000 mg/g; referred to as the overlap population); and the proposed incremental population included in the table above.

1.3 Empagliflozin is currently listed on the PBS for chronic kidney disease (CKD) in patients with eGFR 25 to 75 mL/min/1.73 m^2 and UACR 200 to 5000 mg/g (referred to as the

"cost-minimisation approach versus dapagliflozin (overlap population)", recommended at the November 2023 PBAC meeting).

2 Background

Registration status

2.1 Empagliflozin was TGA registered in February 2024 for the following indication: to reduce the risk of kidney disease progression in adults with chronic kidney disease (CKD Stages 2 and 3A with UACR ≥30 mg/g, or CKD Stages 3B, 4 and 5 irrespective of UACR).

2.2 Empagliflozin is also currently TGA registered for treatment of the following conditions:

- Type 2 diabetes mellitus (T2DM) as monotherapy or combination therapy.
- T2DM with established cardiovascular disease to reduce the risk of cardiovascular death, in combination with standard care.
- Symptomatic heart failure, independent of left ventricular ejection fraction, adjunctive to standard care.

Previous PBAC consideration

2.3 Empagliflozin was listed on the PBS for the following restrictions:

- Type 2 diabetes in combination with metformin and/or a sulfonylurea, or in combination with insulin, or in combination with metformin and a gliptin.
- Symptomatic New York Heart Association class II, III, or IV chronic heart failure.
- CKD with an eGFR 25 to 75 mL/min/1.73 m^2, and a UACR 200 to 5000 mg/g.

2.4 The PBAC considered empagliflozin for chronic kidney disease at the November 2023 meeting for the population proposed in the current resubmission. At that time, the PBAC only recommended empagliflozin for the treatment of CKD in the same population as PBS-listed dapagliflozin (overlap population), on the basis of a cost-minimisation approach versus dapagliflozin.

2.5 The PBAC did not recommend listing of empagliflozin for the incremental population. Table 2, below summarises the key matters of concern from the November 2023 PBAC meeting for the incremental population.

Table 2: Summary of key matters of concern

Matter of concern	How the resubmission addresses it
Restriction	
The PBAC considered that any resubmission for empagliflozin for a broader population should reconsider which subgroups are nominated and ensure they include significantly high UACR (paras 7.16 and 7.24).	The incremental population requested in the proposed expanded restriction is unchanged from the November 2023 submission, and includes patients with moderately increased and high risk of disease progression, and patients with UACR <200 mg. The resubmission argued that the subgroup analyses by KDIGO risk categories considered by the PBAC at the November 2023 meeting were not powered for the composite endpoint, had small sample sizes, and were not reliable evidence of differences in efficacy between risk categories. It also argued that moderate to high KDIGO risk category subgroups experienced slower disease progression, and given the short EMPA-KIDNEY trial duration and follow up, it was unlikely that the primary composite outcome would capture the long-term benefits of empagliflozin. Therefore, it was argued that the results for the incremental population as a whole, should be preferred. The resubmission noted that Australian and international clinical guidelines recommend the use of SGLT2 inhibitors across a broad range of risk of CKD progression, and this was consistent with expert opinion presented in the submission supporting the use of SGLT2 inhibitors in early CKD.
Clinical evaluation	
The PBAC did not consider the submission adequately demonstrated a benefit in the incremental population (para 7.21). The PBAC considered the empagliflozin resulted in little or no improvement in patients categorised as low, moderate and high risk (KDIGO staging), or with UACR <200mg/g at baseline (para 7.16 and 7.20).	The clinical evidence presented in the resubmission was largely unchanged, and additional analyses based on disaggregated risk groups within the incremental subgroup were not presented. The resubmission presented additional *post hoc* subgroup analyses of the ITT population by baseline UACR (<200 mg/g; ≥200 mg/g) and *post hoc* analyses of the incremental population used to inform the economic model.
Economic evaluation	
The PBAC did not find the economic model informative to support a listing for the incremental population and noted a number of issues, including treatment effects and transition probabilities that were not representative of the incremental population, the inclusion of a large proportion of patients with diabetes (50.5%) and heart failure (12.5%), as well as patients outside of the proposed restriction (10.2%), changes in eGFR and UACR that did not account for within-patient variation and collinearity, extrapolated treatment effects that did not account for the natural history of CKD, unsupported assumptions about discontinuation of ACEi/ARB treatment, and largely uninformative sensitivity analyses (para 6.69, 6.82, 7.22).	The resubmission acknowledged PBAC's concerns with the economic model used in the November 2023 submission, and completely revised the economic evaluation, based on the model structure used in the July 2021 dapagliflozin submission.

Matter of concern	How the resubmission addresses it
Utilisation and financial impact of listing	
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 (para 7.23).	Details on the projected size of the incremental population sub-populations were not provided in the resubmission. The resubmission assumed higher uptake rates for empagliflozin in the incremental population.
DUSC noted a number of uncertainties with the financial estimates, including: - Uncertainty in the Australian prevalence of CKD. - The potential overestimate of the proportion of patients eligible for empagliflozin (without diabetes). - The overestimate of the proportion of patients diagnosed with CKD. - Uncertainty in estimates of the size of the incremental population from the National Health Measures Survey (NHMS) dataset - The underestimate of the uptake rates in the incremental population (para 6.94).	In the revised financial implications presented in the resubmission: - The estimated prevalence of CKD is unchanged. - The proportion of patients eligible for empagliflozin without diabetes has been revised. - The proportions of patients diagnosed with CKD over time have been increased. - The size of the incremental population has been revised, based on the average of the NHMS estimate and results of an Australian retrospective cohort analysis (Neuen 2023). - Higher uptake rates are assumed in the resubmission.

Source: Empagliflozin Public Summary Document, November 2023 PBAC meeting; Sections 1 to 4 of the resubmission.
Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; PBAC, Pharmaceutical Benefits Advisory Committee; PSD, Public Summary Document; UACR, urine albumin-creatinine ratio.

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

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics.

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
EMPAGLIFLOZIN					
empagliflozin 10 mg tablet, 30	14092Q	1	30	5	Jardiance
Restriction Summary / Treatment of Concept					
Category / Program: ☒ GENERAL - General Schedule (Code GE)					
Prescriber type: ☒Medical Practitioners ☒Nurse practitioners					
Restriction type: ☒Authority Required (Streamlined) [new/existing code]					
	Administrative Advice: **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 Practitioners.				
	Administrative Advice: *No increase in the maximum quantity or number of units may be authorised.*				
	Administrative Advice: *No increase in the maximum number of repeats may be authorised.*				
Episodicity: Chronic					
Severity: n/a					
Condition: Kidney disease					

Indication: Chronic kidney disease
Treatment Phase: n/a
Clinical criteria:
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
AND
Clinical criteria:
Patient must have an estimated glomerular filtration rate of between 20 to 90 mL/min/1.73 m2 inclusive prior to initiating treatment with this drug
AND
Clinical criteria:
Patient must have a urinary albumin to creatinine ratio of at least 200 mg/g (22.6mg/mmol) if the patient has an estimated glomerular filtration rate of between 45 to 90 mL/min/1.73 m^2 inclusive prior to initiating treatment with this drug
AND
Clinical criteria:
Patient must discontinue treatment with this drug prior to initiating renal replacement therapy, defined as dialysis or kidney transplant
AND
Clinical criteria:
Patient must not be receiving treatment with another sodium-glucose co-transporter 2 (SGLT2) inhibitor
AND
Clinical criteria:
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
Prescribing Instructions: 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.

3.2 The resubmission requested a dispensed price for empagliflozin 10 mg of $58.85 (DPMQ per 1 pack of 30 tablets), and $104.24 assuming 60 day dispensing (DPMQ per 2 packs of 30 tablets). Empagliflozin for CKD is not currently authorised for 60 day dispensing.

3.3 As of October 2024, the PBS listed AEMP for empagliflozin 10mg was $44.44. The requested AEMP ($42.22) in the submission was consistent with the expected PBS listed AEMP of empagliflozin for the treatment of diabetes, chronic heart failure and CKD, incorporating the April 2025 5% 10-year anniversary statutory price reduction. The pre-sub-committee response (PSCR) indicated that effective 1 April 2025, the T2DM listing for empagliflozin would be expanded to include patients who are at high cardiovascular (CV) risk, have existing CV disease or identify as Aboriginal or Torres Strait Islander, without the requirement to meet a specific glycaemic target. This expanded listing was associated with a further price reduction for empagliflozin 10 mg with a new AEMP of $39.02 (12.2% reduction overall from the October AEMP of $44.44).

3.4 The proposed expanded restriction is narrower than the 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).

3.5 The proposed expanded restriction is based on the current PBS listing for empagliflozin and dapagliflozin for the treatment of CKD (eGFR 25 to 75 mL/min/1.73 m^2 with UACR 200 to 5,000 mg/g; overlap population), with the addition of the aggregated incremental subgroups included in the key clinical trial (EMPA-KIDNEY):

- eGFR 20 to <25 mL/min/1.73 m^2, regardless of UACR.
- eGFR 25 to <45 mL/min/1.73 m^2 with UACR <200 mg/g.
- eGFR 25 to 75 mL/min/1.73 m^2 with UACR >5,000 mg/g.
- eGFR >75 to 90 mL/min/1.73 m^2 with UACR ≥200 mg/g.

3.6 The PBAC previously considered that the *post hoc* subgroup analyses of the EMPA-KIDNEY trial did not adequately demonstrate a benefit in the broadened indication for CKD, and that empagliflozin demonstrated little or no improvement in patients categorised as low, moderate and high risk (KDIGO staging) or in those patients with UACR <200 mg/g. The PBAC considered that any resubmission for empagliflozin for a broader population should reconsider which subgroups are nominated and ensure they include significantly high UACR (paras 7.16 and 7.24, Empagliflozin Public Summary Document (PSD), November 2023 PBAC meeting). The incremental population requested in the proposed expanded restriction is unchanged from the November 2023 submission, which includes patients with moderately increased and high risk of disease progression, and patients with UACR <200 mg/g. The pre-PBAC argued that the EMPA-KIDNEY trial demonstrated a significant benefit in a diverse population of CKD patients including those with little to no albuminuria and highlighted that empagliflozin had the broadest CKD indication approved by the TGA of all of the SGLT2 inhibitors, based on the EMPA-KIDNEY trial evidence.

3.7 The PSCR disagreed with the suggestion in the commentary that an SGLT2 inhibitor class effect exists for CKD given the absence of supporting RCT evidence, and does not support broadening the PBS listing for dapagliflozin in CKD (to include the incremental population) as there is currently no Level 1 randomised controlled trial (RCT) evidence supporting its use in the wider CKD population and because of misalignment with the approved TGA indication for patients with proteinuric CKD. The ESC acknowledged that expanding the dapagliflozin listing would be outside the available trial evidence for dapagliflozin, however it considered the benefits of SGLT2 inhibitors in CKD are generally accepted to be a class effect (see paragraph 4.11) and having different PBS listings within the same patient population would require further consideration. The pre-PBAC response noted that dapagliflozin was only TGA approved for use in

proteinuric CKD, which was consistent with the available clinical trial evidence in the DAPA-CKD trial.

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, 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/vaping, age ≥60 years, Aboriginal and Torres Strait Islander descent; CKD Management in Primary Care (5th edition, Kidney Health Australia, 2024)).

4.2 A diagnosis of CKD is defined as having one or both of the following criteria, irrespective of underlying cause (Kidney Health Australia 2024, CKD Management in Primary Care):

- An estimated or measured GFR of <60 mL/min/1.73 m^2 that is present for 3 months or more with or without evidence of kidney damage.
- Evidence of kidney damage (albuminuria, haematuria, structural abnormalities, pathological abnormalities) with or without a decrease in GFR, that is present for 3 months or more.

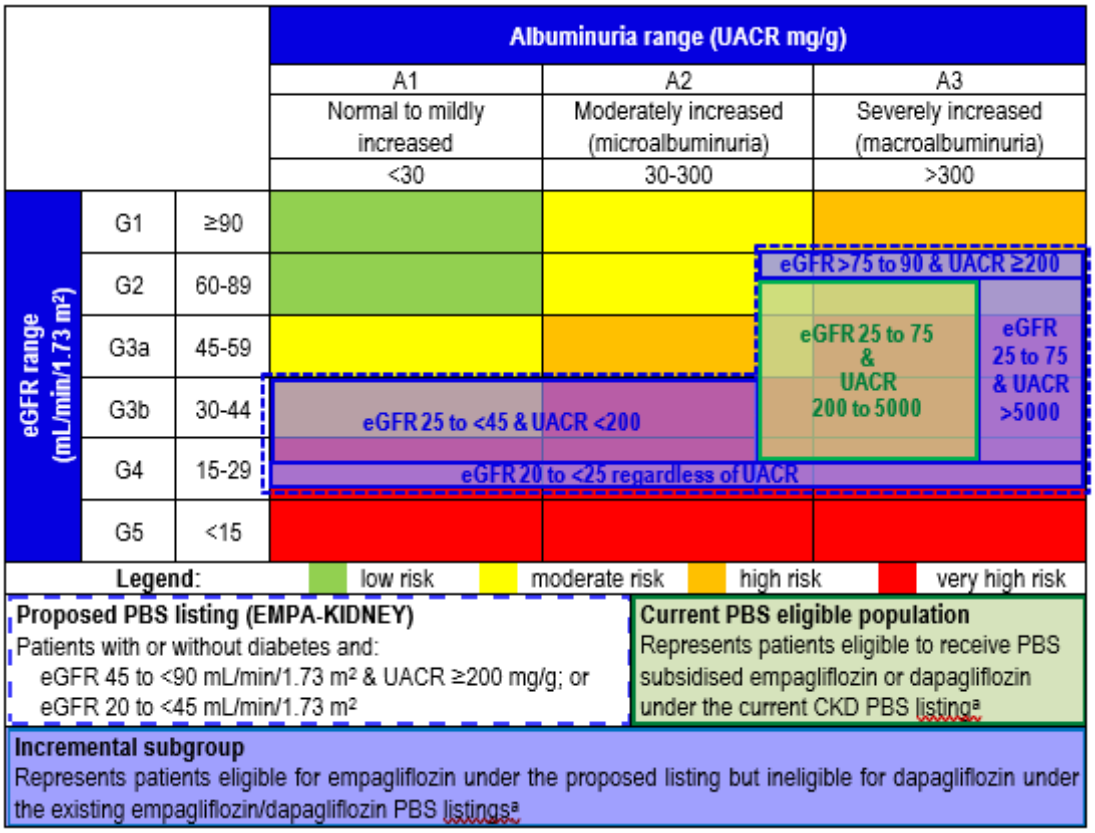
4.3 The prevalence of CKD in the Australian population is not known, but available data suggests that one in seven (14.2%) adults had indicators of chronic kidney disease, up from 10.8% a decade earlier; only 7.4% of people aged 18 years and over who had indicators of CKD self-reported having kidney disease. (National Health Measurement Survey NHMS *2022–24*). The PBAC noted that Aboriginal and Torres Strait Islanders had 4 times higher incidence of ESKD, higher rates of conservative management of the disease and 4 times higher rates of mortality and were thus likely to experience an increased absolute benefit from use of an SGLT2 inhibitor[1].

4.4 Approximately 10% of the Australian population with biomedical signs of CKD are diagnosed, with diagnosis typically delayed until progression to CKD stage 3–4 disease when symptoms of kidney disease are more apparent (AIHW 2023a). The severity of CKD and the risk of progression to end-stage kidney disease (ESKD) or cardiovascular death can be assessed using the Kidney Disease Improving Global Outcomes (KDIGO) classification of CKD prognosis.

4.5 Figure 1 describes the proposed population in terms of KDIGO risk classification.

[1] AIHW, 2011, 2020

Figure 1: Summary of the proposed PBS population and subgroups



Source: KDIGO (2024); Figure 1, para 4.4 of the empagliflozin PSD, November 2023 PBAC meeting.
Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; PBS, Pharmaceutical Benefits Scheme; SC, standard care; PSD, Public Summary Document; UACR, urine albumin to creatinine ratio.
[a] Current empagliflozin (PBS item 14092Q) and dapagliflozin (PBS item 13106T) PBS listing for the treatment of CKD.

4.6 The incremental population includes a broad amalgam of patients with substantial variation in eGFR and UACR characteristics, and hence baseline risk of CKD progression (ranging from moderately increased risk to very high risk). The pre-PBAC response from the sponsor argued that the proposed PBS incremental CKD population was at equally high risk of kidney disease progression and cardiovascular (CV) complications as the currently reimbursed CKD population. It noted that while patients with lower albuminuria levels typically experience a slower rate of kidney function decline, several studies have demonstrated a significantly elevated risk of kidney disease progression and adverse mortality outcomes. Input emphasised that there was a high clinical need for early treatment initiation with empagliflozin before patients experience significant kidney disease progression.

4.7 Empagliflozin is a selective sodium-glucose co-transporter-2 (SGLT2) inhibitor widely used for the treatment of adults with type 2 diabetes. 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), that 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 angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB).

4.9 The proposed clinical management algorithm positions empagliflozin as adjunctive therapy for the incremental population, in addition to the use of empagliflozin or dapagliflozin as adjunctive therapy for patients with eGFR 25 to 75 mL/min/1.73m^2 and UACR 200 to 5,000 mg/g, consistent with the current PBS listing for SGLT2 inhibitors for CKD.

4.10 The Kidney Health Australia (KHA) 2024 guidelines recommend the use of SGLT2 inhibitors in patients with a moderate, high or very high risk of CKD progression (although not to initiate if eGFR < 25 mL/min/1.73m^2). See Figure 1 for details of risk classification. Similarly, the Caring for Australians and New Zealanders with Kidney Impairment (CARI) 2024 guidelines recommend the use of SGLT2 inhibitors in patients with a moderate, high or very high risk of CKD progression. However, the KHA (2024), KDIGO (2024) and CARI (2024) CKD risk classifications differ in their respective definitions of very high risk:

- macroalbuminuria (UACR>30mg/mmol) regardless of eGFR OR eGFR<30 for KHA
- eGFR 45-59 and UACR > 30mg/mmol; OR eGFR 30-44 and UACR >= 3; OR eGFR <30 for KDIGO
- macroalbuminuria (males UACR > 25 mg/mmol, females UACR > 35 mg/mmol) regardless of eGFR; OR eGFR<30 for CARI

4.11 Both the KHA and CARI guidelines for Australia recommend the use of SGLT2 inhibitors in patients with eGFR <30 mL/min/1.73 m2 (when indicated), with appropriate consideration of recommendations in the respective Product Information Documents not to initiate treatment with empagliflozin in patients with an eGFR <20 mL/min/1.73m2, or initiate dapagliflozin in patients with an eGFR <25 mL/min/1.73m2.

4.12 The benefits of SGLT2 inhibitors in CKD are generally accepted to be a class effect (Roddick et al. 2023; Bailey et al. 2022; Schmidt et al. 2021). Australian (KHA 2024, CARI 2024) and international clinical CKD guidelines (UK Kidney Association 2023; European Kidney Association 2023) treat the efficacy of SGLT2 inhibitors in CKD as a class effect and recommend the use of SGLT2 inhibitors across a range of risks of CKD progression, encompassing a broader population than the proposed restriction. The pre-PBAC response noted that, based on available clinical trial evidence, dapagliflozin

is only TGA approved for use in patients with proteinuric CKD while the TGA approval for empagliflozin allows use in patients with low and high albuminuria.

4.13 The resubmission noted Australian expert clinician advice that the omission of the incremental population leaves a high unmet clinical need for empagliflozin in patients who are mostly at high to very high risk of kidney disease progression and cardiovascular complications, and that expanding the current PBS listing for empagliflozin to reflect the broader patient population from EMPA-KIDNEY would align with recently updated guidance on SGLT2 inhibitors in local and international CKD guidelines (see Australian and New Zealand Society of Nephrology letter of support, Appendix 1 of the resubmission).

4.14 The PBAC noted Australian and international guidelines (KDIGO, 2024; UK Kidney Association, 2023; European Kidney Association, 2023) were recently updated to include the use of SGLT2 inhibitors in the treatment of CKD.

Table 3: Clinical guidelines for use of SGLT2 inhibitors in CKD

Source	Recommendation for use of SGLT2 inhibitors in CKD (in combination with RAS medication; not requiring RRT)	Level of recommendation
Australia		
Kidney Health Australia (2024)[a]	CKD with moderate risk of disease progression: - eGFR ≥60 mL/min/1.73 m^2 with microalbuminuria; or - eGFR 45-59 mL/min/1.73 m^2 with normoalbuminuria.	NR
	CKD with high risk of disease progression: - eGFR 30-59 mL/min/1.73 m^2 with microalbuminuria; or - eGFR 30-44 mL/min/1.73 m^2 with normoalbuminuria.	
	CKD with very high risk of disease progression: - macroalbuminuria irrespective of eGFR; or - eGFR <30 mL/min/1.73 m^2 irrespective of albuminuria.	
	Recommended for use in people with CKD and proteinuria, with or without diabetes, to reduce the risk of progressive decline in kidney function. Initiating an SGLT2 inhibitor in patients with an eGFR <25 mL/min/1.73m^2 was not recommended due to limited evidence.	
CARI (2024)[b]	CKD with moderate risk of disease progression: - eGFR 60->90 mL/min/1.73m^2 and UACR 3-30 mg/mmol (30-300 mg/g) (microalbuminuria); or - eGFR 45-59 mL/min/1.73m^2.	Weak
	CKD with high risk of disease progression: - eGFR 60->90 mL/min/1.73m^2 and UACR >30 mg/mmol (>300 mg/g) (macroalbuminuria); or - eGFR 30-44 mL/min/1.73m^2 and UACR 3-30 mg/mmol (30-300 mg/g) (microalbuminuria); or - eGFR <30 mL/min/1.73m^2.	Strong
	CKD with very high risk of disease progression: - eGFR 45-59 mL/min/1.73m^2 and UACR >30 mg/mmol (>300 mg/g) (macroalbuminuria); or - eGFR 30-44 mL/min/1.73m^2 and UACR 3-30 mg/mmol (30-300 mg/g) (microalbuminuria); or - eGFR <30 mL/min/1.73m^2.	Strong
International		

Source	Recommendation for use of SGLT2 inhibitors in CKD (in combination with RAS medication; not requiring RRT)	Level of recommendation
KDIGO Working Group (2024)[c]	CKD with T2DM: - eGFR ≥20 mL/min/1.73 m^2; or	1A
	CKD: - eGFR ≥20 mL/min/1.73 m^2 and UACR ≥20 mg/mmol (≥200 mg/g); or - heart failure, irrespective of level of albuminuria.	1A
	CKD: - eGFR 20 - 45 mL/min/1.73 m^2 and UACR <20 mg/mmol (<200 mg/g).	2B
UK Kidney Association (2023)[d]	CKD with T2DM: - eGFR 20 - 45 mL/min/1.73m^2; or - eGFR >45 mL/min/1.73m^2 and UACR ≥25 mg/mmol; or - eGFR >45 - 60 mL/min/1.73m^2 and UACR <25 mg/mmol. - Consider use of an SGLT2 inhibitor if eGFR <20 mL/min/1.73 m^2 to slow rate of disease progression.	1A 1A 2B 2B
	CKD without T2DM: - eGFR ≥20 mL/min/1.73m^2 and UACR ≥25 mg/mmol irrespective of primary kidney disease; or - eGFR 20 - 45 mL/min/1.73m^2 and UACR <25 mg/mmol. - Consider use if eGFR <20 mL/min/1.73 m^2 to slow rate of disease progression.	1A 1B 2B
European Renal Association (2023)[e]	CKD with diabetes mellitus: - eGFR 20 - 60 mL/min/1.73 m^2; or - UACR >3.39 mg/mmol (>30 mg/g).	NR
	CKD without diabetes mellitus: - eGFR 45 - 90 mL/min/1.73 m^2 and UACR ≥20 mg/mmol (≥200 mg/g); or - heart failure, irrespective of level of albuminuria.	
	CKD: - eGFR 20 - 45 mL/min/1.73 m^2 and UACR <20 mg/mmol (<200 mg/g).	

Source: Section 1.2, pp47-54 of the resubmission.
Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SGLT2, sodium-glucose co-transporter 2;
[a] Chronic Kidney Disease Management in Primary Care, Kidney Health Australia (2024).
[b] CARI Guidelines: Australian and New Zealand living guideline for chronic kidney disease (2024).
[c] KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (2024).
[d] Roddick et al. (2023), UK Kidney Association Clinical Practice Guideline: Sodium-Glucose Co-transporter-2 (SGLT-2) Inhibition in Adults with Kidney Disease 2023 UPDATE.
[e] Mark et al. (2023), SGLT2i for evidence-based cardiorenal protection in diabetic and non-diabetic chronic kidney disease.

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

5 Comparator

5.1 The resubmission nominated placebo (add-on to standard care) as the main comparator. Standard care was defined as including treatment with an ACE inhibitor or ARB, consistent with current clinical practice in the Australian setting and the treatment regimen used in the key clinical trial (EMPA-KIDNEY).

5.2 The PBAC previously accepted placebo as the appropriate comparator for the incremental population (para 7.19, empagliflozin PSD, November 2023 PBAC meeting).

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician noted published evidence of ongoing benefit in people randomised to the active arm of the EMPA-KIDNEY trial during two years of extended follow up.[2] It was noted event rates approximately doubled in this extended follow up period compared to those observed at conclusion of the trial, and people with low levels of albuminuria benefited from ongoing treatment.

6.2 The PBAC considered that the hearing was supportive of the evidence provided in the submission.

Consumer Comments

6.3 The PBAC noted and welcomed the input from two health care professionals as well as one consumer group and one medical organisation via the Consumer Comments facility on the PBS website. The comments from the health care professionals supported the reimbursement for empagliflozin specifically and SGLT2i medications more generally to delay progression of kidney disease. The benefits of treatment described included rescuing residual kidney function, reducing other morbidities and reducing the costs of dialysis.

6.4 The Australian Diabetes Society supported the indication of all SGLT2 inhibitors available in Australia to include CKD, according to the study outcome data — an eGFR down to 20 ml/min/1.73 m^2 or an albumin to creatinine ration above 200 mg/g if eGFR is above 45 ml/min/1.73 m^2. The input further described benefits on the economy of expanding and funding SGLT2 inhibitors for CKD noting that according to AIHW (2023), $1.9 billion health system expenditure in 2020–21 was attributable to CKD.

6.5 Kidney Health Australia expressed support for an expanded listing for empagliflozin noting that all patients with CKD are at increased risk of disease progression and adverse cardiovascular outcomes and this extends to the population of CKD patients who currently do not have reimbursed access to SGLT2 inhibitors. Despite the poor prognosis, the broader CKD population have limited access to effective treatments that can modify their disease course.

6.6 The PBAC recollected the input from NACCHO for this item in November 2023 and noted the high incidence of disease amongst Aboriginal and Torres Strait Islander Peoples and the challenges to accessing renal physicians and lower transplant rates

[2] Herrington WG et al., 2025, Long-Term Effects of Empagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med.*;392(8): 777-787

and therefore the additional benefits to be gained from increasing public funded treatment options for this population

Clinical trials

6.7 The resubmission presented results of the EMPA-KIDNEY trial overall ITT population, and post hoc subgroup analyses of the EMPA-KIDNEY trial for the currently reimbursed overlap population, and the proposed PBS incremental population. These analyses were previously considered by the PBAC at the November 2023 meeting.

6.8 In addition, the resubmission presented new *post hoc* analyses of the EMPA-KIDNEY trial not previously considered by the PBAC:

- Post hoc subgroup analyses of the primary and key secondary outcomes by baseline albuminuria (UACR <200 mg/g and UACR ≥200 mg/g).
- Post hoc subgroup analyses of outcomes informing the economic analysis, for the proposed incremental subgroup, ITT population and UACR subgroups.

6.9 Details of the trial presented in the resubmission are provided in Table 4.

Table 4: Trial and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
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.	Clinical Study Report, 28 October 2022.
	Herrington WG, Staplin N, Wanner C, et al. Empagliflozin in patients with chronic kidney disease.	*New England Journal of Medicine* 2023, 388(2):117-127.
	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.	*Clinical Kidney Journal* 2018, 11(6):749-761.
	Herrington WG, Wanner C, Green JB, et al. Design, recruitment, and baseline characteristics of the EMPA-KIDNEY trial.	*Nephrology Dialysis Transplantation* 2022, 37(7):1317-1329.

Source: Table 2.1, p78 of the resubmission; pp80-83, Section 2.2 of the resubmission.

6.10 The key features of the EMPA-KIDNEY trial are summarised in Table 5.

Table 5: 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^2; or eGFR 45 to <90 mL/min/1.73 m^2 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^2, ESKD, or CV death. Secondary outcomes: all-cause mortality, CV mortality, ESKD, other renal/CV outcomes and safety.	*Post hoc* subgroup analyses of time to ESKD (excluding patients who died without ESKD), time to death (for patients without ESKD), and time from ESKD to death (for patients with ESKD) in the incremental subgroup.

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; 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 EMPA-KIDNEY 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 type 2 diabetes (49.0%, 38.4%, 44.4%), cardiovascular disease (32.0%, 19.7%, 26.7%) and heart failure (12.5%, 6.5%, 10.0%). 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%) compared to the overlap and overall ITT populations.

6.13 The incremental population is comprised of a broad range of populations with different baseline eGFR and UACR levels, with risks of disease progression ranging from moderately increased risk to very high risk. The resubmission compared the patient demographic and disease characteristics from the EMPA-KIDNEY trial incremental subgroup with those from an Australian retrospective cohort analysis of patients matching the EMPA-KIDNEY incremental population in terms of eGFR and UACR (Neuen 2023). Although there were limitations of the Neuen 2023 analysis (based on selected patients captured in the MedicineInsight database; a large proportion of potentially relevant patients with no UACR measurement were excluded), the results suggest that the largest eligible population group in the Australian setting (eGFR >75 to 90 mL/min/1.73 m^2 and UACR ≥200 mg/g; 46.4%) may be the incremental population with the lowest risk of CKD progression, who were sparsely represented in the EMPA-KIDNEY incremental population (approximately 5%).

6.14 The incremental population in the EMPA-KIDNEY trial included a large proportion of patients with diabetes (49.0%) and heart failure (12.5%) who are likely to be eligible for treatment under existing SGLT2 inhibitor PBS listings. Pre-specified subgroup analyses showed potential treatment effect interactions by baseline diabetes status, with decreasing treatment effect in patients without diabetes. It was unclear whether heart failure was a treatment effect modifier given the wide confidence intervals for treatment effects in the subgroup with heart failure. Overall, the available data is

indicative of potential differences in terms of baseline risk and treatment effects between the trial and the Australian setting, which are likely to impact the magnitude of benefit associated with empagliflozin in addition to standard care.

Comparative effectiveness

Key outcomes for the EMPA-KIDNEY ITT, overlap, incremental and baseline UACR populations

6.15 Table 6 summarises the results of the primary and key secondary outcomes of the EMPA-KIDNEY trial in the ITT population, post hoc overlap and incremental populations, as well as the new post hoc subgroup analyses by baseline albuminuria (UACR <200 mg/g; UACR ≥200 mg/g).

Table 6: *Post hoc* subgroup analyses of the primary and key secondary outcomes of EMPA-KIDNEY

Population or subgroup	Empagliflozin + SC n/N (%)	Placebo + SC n/N (%)	Hazard ratio (95% CI)
Primary composite outcome CKD progression or CV death[a]			
Overall ITT population	432/3304(13.1%)	558/3305(16.9%)	**0.72 (0.64, 0.82)**
Overlap population	184/1446 (12.7%)	227/1397 (16.2%)	**0.76 (0.63, 0.92)**
Incremental population	248/1858 (13.3%)	331/1906 (17.3%)	**0.76 (0.65, 0.90)**
UACR <200 mg/g	92/1,361 (6.8%)	108/1,366 (8.0%)	0.87 (0.66, 1.15)
UACR ≥200 mg/g	340/1,943 (17.5%)	450/1,949 (23.1%)	**0.71 (0.62, 0.82)**
Time to first CKD progression[a]			
Overall ITT population	384/3,304 (11.6%)	504/3,305 (15.2%)	**0.71 (0.62, 0.81)**
Overlap population	170/1,446 (11.8%)	212/1,397 (15.2%)	**0.75 (0.61, 0.92)**
Incremental population	214/1,858 (11.5%)	292/1,908 (15.3%)	**0.75 (0.62, 0.89)**
UACR <200 mg/g	63/1,361 (4.6%)	76/1,366 (5.6%)	0.85 (0.61, 1.18)
UACR ≥200 mg/g	321/1,943 (16.5%)	428/1,949 (22.0%)	**0.70 (0.61, 0.81)**
Time to first adjudicated CV death[a]			
Overall ITT population	59/3,304 (1.8%)	69/3,305 (2.1%)	0.84 (0.60, 1.19)
Overlap population	18/1,446 (1.2%)	19/1,397 (1.4%)	0.89 (0.46, 1.69)
Incremental population	41/1,858 (2.2%)	50/1,908 (2.6%)	0.83 (0.55, 1.25)
UACR <200 mg/g	NR	NR	NR
UACR ≥200 mg/g	NR	NR	NR
Time to adjudicated all-cause mortality[a]			
Overall ITT population	148/3,304 (4.5%)	167/3,305 (5.1%)	0.87 (0.70, 1.08)
Overlap population	51/1,446 (3.5%)	47/1,397 (3.4%)	1.02 (0.69, 1.52)
Incremental population	97/1,858 (5.2%)	120/1,908 (6.3%)	0.82 (0.63, 1.07)
UACR <200 mg/g	81/1,361 (6.0%)	90/1,366 (6.6%)	0.91 (0.67, 1.23)
UACR ≥200 mg/g	67/1,943 (3.4%)	77/1,949 (4.0%)	0.83 (0.60, 1.15)

Source: Tables 2.26-2.32, pp146-162, and Tables 2.40-2.45, pp186-203 of the resubmission.

Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; CI, confidence interval; eGFR, estimated glomerular filtration rate; EPI, epidemiology collaboration formula; ESKD, end-stage kidney disease; ITT, intention-to-treat; NR, not reported; SC, standard care; UACR, urine albumin to creatinine ratio.

[a] Overlap/incremental subgroups by Cox regression model with terms for age, sex, diabetes status, region, treatment, DAPA−CKD eGFR/UACR inclusion criteria and treatment by DAPA−CKD eGFR/UACR inclusion criteria. UACR < or ≥200 mg/g subgroups by Cox regression model with terms for age, sex, diabetes status, screening eGFR (CKD-EPI), region, treatment, baseline UACR and treatment by baseline UACR. Kidney disease progression included ESKD (initiation of maintenance dialysis or receipt of a kidney transplant), sustained eGFR decline of ≥40% or to <10 mL/min/1.73 m^2 or adjudicated renal death.

Note: Statistically significant results in bold.

Note: Results presented in the previous submission shaded blue.

6.16 In the post hoc subgroup analyses, 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.

6.17 For key secondary outcomes, the post hoc subgroup analyses showed treatment with empagliflozin plus standard care was associated with statistically significant improvements in time to first CKD progression in both the overlap and incremental populations, with a similar magnitude of benefit to the ITT population; however results for time to first adjudicated cardiovascular death and time to adjudicated all-cause mortality did not achieve statistical significance for the ITT, overlap and incremental populations.

6.18 In the subgroup analyses by baseline albuminuria, results for the UACR ≥200 mg/g subgroup showed treatment with empagliflozin was associated with statistically significant improvements in the composite outcome of time to first CKD progression or cardiovascular death and time to first CKD progression compared to placebo. This was similar to results for the ITT population, and overlap and incremental subgroups. However, results for the UACR <200 mg/g subgroup showed no statistically significant difference between treatment with empagliflozin and placebo. Neither UACR subgroup achieved statistical significance for time to adjudicated all-cause mortality. The pre-PBAC response stated that it was important to highlight that patients with lower baseline UACR are a cohort in which the severity of CKD progresses more slowly and therefore are unlikely to have accrued sufficient primary outcome events during the active trial period to demonstrate a significant treatment difference.

6.19 At the November 2023 meeting, 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 albuminuria subgroups (UACR<30, 30-300, and >300 mg/g; p=0.0174) and a near significant treatment effect interaction by baseline diabetes status (yes/no; p=0.0598). There was also a trend of decreasing treatment effect in patients without diabetes or with a lower baseline UACR (UACR ≤300 mg/g) (para 6.24, empagliflozin PSD, November 2023 PBAC meeting). The ESC considered the available data still does not support a clear treatment benefit in patients with low/moderate/high KDIGO risk or in patients with a UACR <200 mg/g. The pre-PBAC response stated that the long-term follow-up study of EMPA-KIDNEY provided clear evidence that people with low levels of albuminuria benefit by being treated with empagliflozin, with subgroup analyses demonstrating a stronger signal of benefit following the additional two years of follow-up in the lower albuminuria subgroups [i.e., uACR < 30 mg/g: HR 0.83 (0.61, 1.13) vs. HR 1.01 (0.66, 1.55) in the active trial period and uACR 30 to 300 mg/g:

HR 0.87 (0.70, 1.09) vs. HR 0.91 (0.65, 1.26) in the active trial period] (Herrington et al, 2025).

6.20 Given the subgroup analyses were conducted post hoc, these results should be interpreted with caution. Subgroup analyses by the incremental population component subgroups were not presented. The PSCR (p1) argued that splitting of the incremental population into smaller subgroups would result in very small patient numbers and uncertain results. The PSCR also noted that the currently reimbursed CKD population had a variable risk of CKD progression yet PBAC did not request disaggregated analyses by risk groups and made a positive recommendation for the entire 'overlap' CKD population (empagliflozin, PSD, November 2023 PBAC meeting). The PSCR argued that, therefore, a similar approach should be adopted when assessing the overall treatment effect for the proposed PBS incremental population. To this end, the PSCR maintained that there was clear evidence of a similar treatment effect in the proposed PBS incremental population compared to the currently reimbursed CKD population and the overall ITT population [HR 0.76 (0.65, 0.90) vs. HR 0.76 (0.63, 0.92) vs. HR 0.72 (0.64. 0.82) p-interaction = 0.9903].

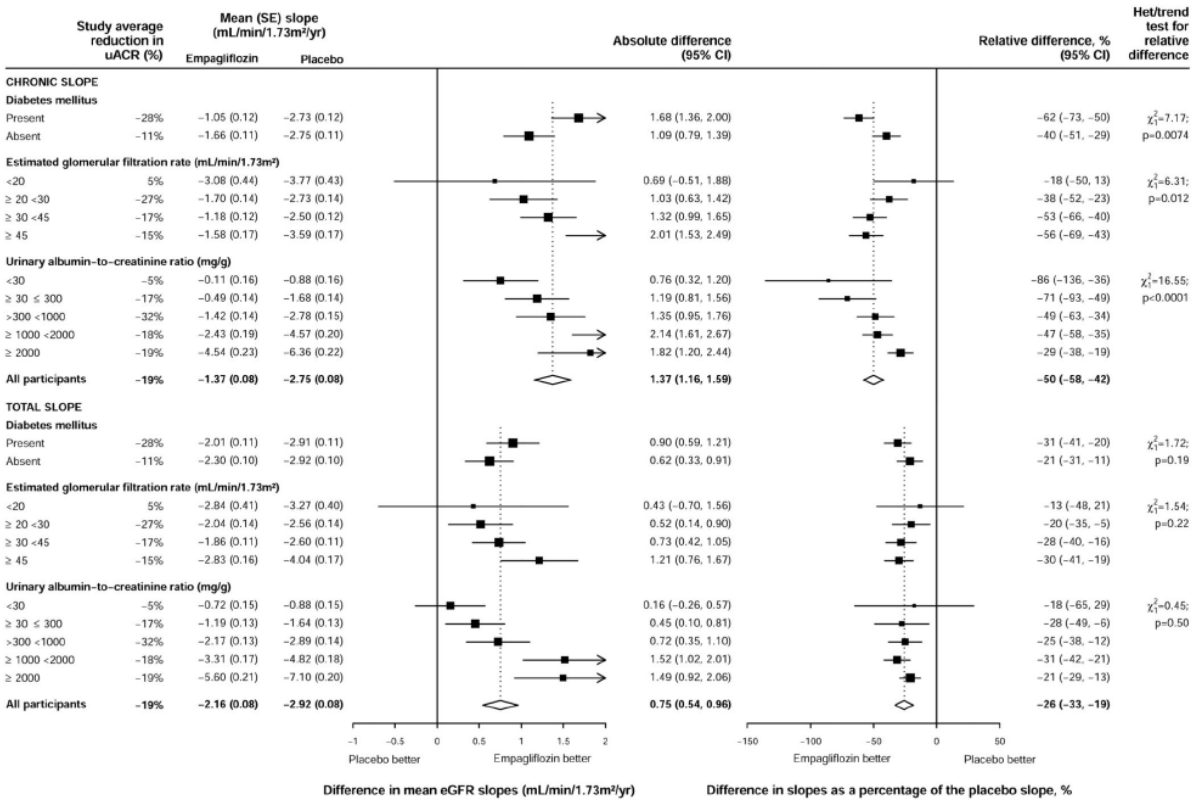
6.21 The pre-PBAC response stated that the eGFR slope was regarded as a more sensitive measure of effect in patients with slowly progressive disease (i.e., UACR < 200 mg/g) and that subgroup analysis by baseline UACR showed a significant reduction in the rate of eGFR decline both in absolute and relative terms to placebo. The response stated this was also consistent with a prespecified secondary analysis that examined the effect of empagliflozin on kidney disease progression in various patient cohorts. The study found that treatment with empagliflozin produced a statistically significant absolute reduction in the chronic eGFR slope across all five uACR categories with an absolute difference in the uACR < 30 mg/g and uACR between 30 and 300 mg/g subgroups of 0.76 and 1.19 mL/min/1.73 m2 per year, respectively (Haynes, 2023). Both these results exceed the claimed minimal clinically important difference (MCID) of 0.75 mL/min/1.73 m2 per year indicating that empagliflozin was effective at meaningfully reducing kidney disease progression in the lower albuminuria subgroups (Grams, 2019).

6.22 The PBAC also noted results from a 2024 Lancet publication[3] that included a pre-specified secondary analysis of the EMPA-KIDNEY trial examining the annualised rate of decline of kidney function (eGFR slope) (see Figure 2). Overall, allocation to empagliflozin slowed the rate of decline in eGFR from 2 months to final follow-up (the chronic slope) by 1.37 mL/min per 1.73 m² per year (95% CI 1·16–1·59), which represented a 50% (42–58%) relative reduction in the mean chronic slope. The PBAC noted Staplin et al concluded empagliflozin slowed the rate of progression of chronic

[3] Staplin, N et al, 'Effects of empagliflozin on progression of chronic kidney disease: a prespecified secondary analysis from the EMPA-KIDNEY trial' *The Lancet Diabetes & Endocrinology*, Volume 12, Issue 1, 39 – 50, January 2024

kidney disease among all types of participant in the EMPA-KIDNEY trial, including those with little albuminuria. It was considered albuminuria alone should not be used to determine whether to treat with an SGLT2 inhibitor.

Figure 2: Absolute and relative effects of allocation to empagliflozin on total slopes and chronic slopes, by prespecified diabetes subgroup, and post-hoc expanded eGFR and uACR subgroups



Source: Staplin, N et al (2024); Figure 2: Absolute and relative effects of allocation to empagliflozin on total slopes and chronic slopes, by prespecified diabetes subgroup, and post-hoc expanded eGFR and uACR subgroups The p value for test of heterogeneity between absolute difference in chronic slopes for patients with and without diabetes is 0·0085, the p value for test for trend in absolute differences in chronic slope across eGFR categories is 0·0013 and that across uACR categories is less than 0·0001. The p value for heterogeneity between absolute differences in total slopes for patients with and without diabetes is 0·19, and the p value for test for trend in absolute differences in total slope across eGFR categories is 0·023 and that across uACR categories is less than 0·0001. eGFR=estimated glomerular filtration rate. uACR=urinary albumin-to-creatinine ratio.

Pre-specified EMPA-KIDNEY subgroup analyses and *post hoc* subgroup analyses by KDIGO stage

6.23 At the November 2023 meeting, 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 (yes/no; 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) (para 6.24, empagliflozin PSD, November 2023 PBAC meeting).

6.24 The PBAC also considered at the November 2023 meeting, that the results of post hoc subgroup analyses of the primary composite outcome in the EMPA-KIDNEY trial by baseline KDIGO risk category provided confirmation of KDIGO staging (based on UACR and eGFR) to predict prognosis and that 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, or in patients with UACR <200 mg/g (para 7.20, empagliflozin PSD, November 2023 PBAC meeting).

6.25 The resubmission acknowledged the diversity of the incremental population, but suggested that almost all patients in the subgroup had a high to very high risk of kidney disease progression, and on that basis, were sufficiently homogeneous for meaningful subgroup analyses. The incremental population included a broad amalgam of patients with substantially variable baseline risk of CKD progression (moderate to very high risk) and was not homogeneous in terms of risk of disease progression. Compared to the ITT population, there were more patients with moderate to high risk and fewer patients with very high risk in the incremental subgroup.

6.26 Table 7 presents the results of *post hoc* subgroup analyses by KDIGO baseline risk category for the primary composite outcome in the EMPA-KIDNEY ITT population.

Table 7: Results of the post hoc subgroup analyses by KDIGO baseline risk category for the primary composite outcome in the EMPA-KIDNEY ITT population

Population or subgroup	eGFR (mL/min/1.73 m²)	UACR (mg/g)	Empagliflozin + SC n/N (%)	Placebo + SC n/N (%)	Hazard ratio (95% CI)
Moderate risk					
G2A2	60-89	30-300	1/55 (1.8%)	1/43 (2.3%)	NR
G3aA1	45-59	<30	NR (N=78)	NR (N=71)	NR
High risk					
G2A3	60-89	>300	14/175 (8.0%)	16/188 (8.5%)	0.83 (0.40, 1.69)
G3aA2	45-59	30-300	5/112 (4.5%)	5/111 (4.5%)	NR
G3bA1	30-44	<30	19/389 (4.9%)	15/400 (3.8%)	1.40 (0.71, 2.77)
Very high risk					
G3aA3	45-59	>300	20/256 (7.8%)	40/260 (15.4%)	**0.47 (0.27, 0.80)**
G3bA2	30-44	30-300	33/442 (7.5%)	36/454 (7.9%)	0.93 (0.58, 1.49)
G3bA3	30-44	>300	88/636 (13.8%)	124/607 (20.4%)	**0.67 (0.51, 0.88)**
G4A1	15-29	<30	21/196 (10.7%)	23/189 (12.2%)	0.88 (0.49, 1.59)
G4A2	15-29	30-300	28/308 (9.1%)	36/327 (11.0%)	0.85 (0.52, 1.40)
G4A3	15-29	>300	193/618 (31.2%)	253/627 (40.4%)	**0.69 (0.57, 0.84)**

Source: Table 1.1.2.2, pp19-22 of Att_2_EMPA-KIDNEY post hoc analysis B.pdf, Attachment 2 of the resubmission.
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.
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: The report for the *post hoc* subgroup analyses noted that 321 patients were excluded from the analyses, based on subgroups with fewer than 14 events. *This appears to be referring to patients informing the G2A2 and G3aA2 subgroups (total 321 patients). Estimates for the G3aA1 subgroup were not presented, with no explanation provided in the resubmission.*

6.27 The resubmission argued that the subgroup analyses by KDIGO risk categories may not be reliable as they were insufficiently powered to show statistically significant

differences between arms. The resubmission acknowledged that results in the lower risk subgroups were less favourable to empagliflozin but claimed that the trial duration was short and may not reflect longer term effects in cohorts with slower disease progression.

6.28 While the results generally favoured empagliflozin in the ITT population, it was unclear whether the treatment effects were representative of patients in the incremental subgroup or overlap population who are already eligible on the PBS. The disaggregation of the incremental subgroup according to KDIGO categories may result in relatively small sample sizes and potentially unreliable results.

6.29 The resubmission also argued that some of the moderate to high KDIGO risk category subgroups had results that were less favourable to empagliflozin (i.e. subgroups with normoalbuminuria, UACR <30 mg/g) as these patients experienced slower disease progression, and it was unlikely that the categorical outcomes informing the primary composite endpoint would capture statistically significant benefits of empagliflozin in these patients given the short EMPA-KIDNEY trial duration and follow up. The argument suggests little or no improvement from empagliflozin treatment in these patients over the trial duration, with significant uncertainty regarding longer term effects.

Post hoc analyses of the EMPA-KIDNEY trial used to inform the economic model

6.30 The resubmission presented the results of *post hoc* subgroup analyses used to inform the economic model for time to ESKD (excluding patients who died without ESKD), time to adjudicated death from any cause (for patients without ESKD), and time from ESKD to adjudicated death from any cause (for patients with ESKD).

6.31 The economic model base case was based on the results for the incremental population, with sensitivity analyses presented using the ITT, UACR <200 mg/g and UACR ≥200 mg/g populations. The alternative data used in sensitivity analyses did not appear informative as the ITT population includes patients who are eligible under the existing CKD listing (overlap population), while the UACR <200 mg/g only partially covers the requested incremental population (eGFR 25 to 45 mL/min/1.73 m^2 with UACR <200 mg/g and potentially eGFR 20 to 25 mL/min/1.73 m^2).

6.32 Results of the post hoc subgroup analyses used to inform the economic model are summarised in Table 8.

Table 8: Post hoc subgroup analyses of EMPA-KIDNEY informing the economic model (incremental population)

Population or subgroup	Empagliflozin + SC n/N (%)	Placebo + SC n/N (%)	Hazard ratio (95% CI)
Time to first occurrence of ESKD (excluding patients who died without experiencing ESKD)[a]	77/1,768 (4.4%)	125/1,809 (6.9%)	**0.64 (0.48, 0.85)**
Time to adjudicated death from any cause (for patients without ESKD)[b]	90/1,781 (5.1%)	99/1,783 (5.6%)	0.89 (0.67, 1.18)
Time from first occurrence of ESKD to adjudicated death from any cause[b]	7/77 (9.1%)	21/125 (16.8%)	0.53 (0.19, 1.44)

Source: Additional analyses for CKD modelling R2524, Attachment 9 of the submission.
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; EPI, epidemiology collaboration formula; ESKD, end-stage kidney disease; UACR, urine albumin to creatinine ratio.
[a] Cox regression model with terms for age, sex, screening diabetes status, local screening eGFR (CKD−EPI), region, treatment, baseline UACR and treatment by baseline UACR.
[b] Overall ITT population and incremental subgroup by Cox regression model with terms for age, sex, screening diabetes status, local screening eGFR (CKD−EPI), local screening UACR, region and treatment. UACR < or ≥ 200 mg/g subgroups by Cox regression model with terms for age, sex, diabetes status, screening eGFR (CKD-EPI), region, treatment, baseline UACR and treatment by baseline UACR
Note: Statistically significant results in bold.

6.33 Based on the *post hoc* subgroup analysis, treatment with empagliflozin plus standard care was associated with statistically significantly longer time to first occurrence of ESKD (excluding patients who died without ESKD) compared to placebo plus standard care in the incremental population.

6.34 For time to adjudicated death from any cause for patients without ESKD and time from first occurrence of ESKD to adjudicated death from any cause the *post hoc* subgroup analyses nominally favoured empagliflozin, but did not reach statistical significance.

6.35 Given the subgroup analyses were conducted post hoc, the results should be interpreted with caution. The resubmission did not adequately justify the non-standard approach of excluding patients from time to event analyses rather than censoring. The selected approach did not appear robust as it would result in loss of information (i.e. time at risk) from excluded patients. During the evaluation, analyses of time to event data censoring rather than removing patients without ESKD were requested and provided by the sponsor. There were marginal differences in treatment effects (hazard ratios) and the incidence of events, but this may be due to the relatively low number of events overall, as most patients did not experience an event during the trial.

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 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)

	Empagliflozin + SC N=3,304	Placebo + SC N=3,305
Any pre-specified non-serious adverse event[a] 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[b] 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 resubmission.
Abbreviations: SC, standard care.
[a] Pre-specified 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).
[b] 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.
Note: Results presented in the previous submission shaded blue.

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 The proportions of patients reporting adverse events in the post hoc incremental and overlap subgroups were similar to the EMPA-KIDNEY overall population.

Benefits/harms

6.40 On the basis of the direct evidence presented in the EMPA-KIDNEY trial *post hoc* incremental subgroup, 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 (≥40% decline in kidney function, or progression to ESKD) or death related to cardiovascular causes.
- There would be a similar incidence of adverse events.

Clinical claim

6.41 The submission described empagliflozin plus standard care as superior in terms of effectiveness and non-inferior in terms of safety compared to placebo plus standard care.

6.42 The PBAC previously considered the claim of superior efficacy against placebo in the incremental population was not adequately supported based on the post hoc subgroup analyses 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 (para 6.49 and 7.16, empagliflozin PSD, November 2023 PBAC meeting).

6.43 The ESC previously noted that the absolute magnitude of benefit associated with empagliflozin will vary substantially given the heterogeneous nature of the incremental population that was composed of a broad range of subpopulations with different baseline eGFR and UACR levels. The ESC was particularly concerned about the absolute magnitude of benefit in the moderate to high KDIGO risk subgroup (eGFR 75 to <90mL/min/1.73m^2 and UACR ≥200 mg/g) that was sparsely populated in the trial (approximately 5%) (para 6.45, empagliflozin PSD, November 2023 PBAC meeting). The absolute magnitude of benefit in clinical practice remained uncertain, with analyses in the resubmission indicating that the eGFR 75 to <90 mL/min/1.73m^2 and UACR ≥200 mg/g subgroup may be the largest group in clinical practice (46% of the incremental population).

6.44 The two-year follow up study of EMPA-KIDNEY signalled a benefit in the lower albuminuria subgroups (see paragraph 6.19) and empagliflozin slowed the rate of progression of chronic kidney disease among all types of participant in the EMPA-KIDNEY trial, including those with little albuminuria (see paragraphs 6.21 and 6.22).

6.45 The PBAC previously considered that a claim of non-inferior comparative safety for empagliflozin versus placebo in the incremental population was reasonable (para 6.50, empagliflozin PSD, November 2023 PBAC meeting).

6.46 The PBAC considered that, although there was uncertainty in magnitude of benefit, the claim of superior comparative effectiveness to placebo plus standard care was reasonable and was adequately supported by the data.

6.47 The PBAC considered that the claim of non-inferior comparative safety to placebo plus standard care was reasonable and adequately supported by the data.

Economic analysis

6.48 The resubmission acknowledged PBAC's concerns regarding the economic evaluation presented in the November 2023 empagliflozin submission, and that the overall complexity and uncertainty of the cost-effectiveness analysis made it uninformative (para 7.16, empagliflozin PSD, November 2023 PBAC meeting).

6.49 Consequently, the economic evaluation in the current resubmission was completely revised based on the model structure used in the dapagliflozin submission previously considered by the PBAC at the July 2021 meeting.

6.50 The modelled economic evaluation compared empagliflozin plus standard care (SC) versus SC alone for the treatment of patients with CKD. The economic evaluation was based on *post hoc* analyses of the EMPA-KIDNEY trial for the incremental population, with additional modelled data.

Table 10: Key components of the economic evaluation

Component	Description
Treatments	Empagliflozin plus standard care (ACEi/ARB) versus standard care alone
Time horizon	15 years versus mean follow-up of 23.9 months in EMPA-KIDNEY
Outcomes	Life years, quality-adjusted life years
Methods used to generate results	Markov cohort state transition model with tunnel states
Health states	CKD (stage 2-4), ESKD (conservative care, dialysis, transplant) and death
Cycle length	One month with half-cycle correction
Transition probabilities	EMPA-KIDNEY trial for the incremental population, extrapolated to 15 years using independent parametric functions. CKD to ESKD: based on Kaplan-Meier curves for time to ESKD (excluding patients who died without ESKD) for up to 31 months for empagliflozin + SC and 30 months for SC, extrapolated in both arms using the Weibull function. CKD to death: based on Kaplan-Meier curves for time to death (excluding patients who reached ESKD) for up to 30 months in both arms, extrapolated in both arms using the Weibull function. ESKD to death: based on Kaplan-Meier curves for time from ESKD to death for up to 16 months for empagliflozin + SC and 13 months for SC, extrapolated in both arms using the exponential function. Australian general population mortality (age- and sex-adjusted, sourced from the Australian Bureau of Statistics 2020-2022 life tables) was applied to all patients who were alive in the model.
Utility values	Health state utility values (CKD, ESKD) were based on published estimates from Jesky 2016.
Costs	The cost of empagliflozin was based on the proposed DPMQ; with a reduction in costs over time based on discontinuations in the EMPA-KIDNEY trial extrapolated using a Gompertz function. The cost of standard care was based on the most frequently used ACEi/ARBs in the EMPA-KIDNEY trial. The cost was applied to both treatment arms in patients who had not reached ESKD. Patients were assumed to be 100% compliant to therapy. Disease monitoring costs based on clinician review and monitoring tests required for patients with CKD and ESKD, as per estimates in the Deloitte Access Economics report on the cost of CKD (February 2023). ESKD treatment costs: the proportions of patients using each treatment modality were based on published estimates (Morton 2011; audit of Australian renal units). The costs of conservative management, dialysis and kidney transplant were based on costs reported in the Deloitte Access Economics report (February 2023). Terminal care costs were based on published estimates (Reeve 2018; health care use and costs in the last 6 months of life for elderly Australian DVA clients without a recorded cancer diagnosis).

Source: Section 3.3-3.6, pp290-331 of the resubmission

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; DPMQ, dispensed price maximum quantity; DVA, Department of Veteran's Affairs; ESKD, end-stage kidney disease; SC, standard care

6.51 All patients begin the model in the CKD health state, with eGFR between 20 and 90 mL/min/1.73 m^2. Patients in the CKD health state can remain in their health state, progress to ESKD, or die prior to reaching ESKD. Patients with ESKD may either remain

in their health state or die. The model included tunnel states to track time from entry into the ESKD health state, in order to apply transitions to death from ESKD.

6.52 The PBAC previously noted that the simple model structure in the July 2021 dapagliflozin submission combined different CKD stages into a single CKD health state and single ESKD health state, which did not allow for transitions through CKD stages or between treatment modalities in ESKD. The PBAC considered that the dapagliflozin submission model structure was poorly justified and overly simple. The PBAC also considered the model had a number of other issues with respect to its time horizon, application of treatment persistence, ESKD transitions, ESKD survival and ESKD costs (para 7.8, dapagliflozin PSD, July 2021 PBAC meeting).

6.53 The resubmission acknowledged that there were several issues with the simple model structure, as noted by ESC and PBAC, but claimed that there are insufficient data from the EMPA-KIDNEY trial to reliably inform all possible transitions for each CKD stage for the proposed PBS incremental population. Despite the limitations of the approach, the resubmission claimed that using the same structure provides a relevant frame of reference for establishing the cost-effectiveness of empagliflozin in the proposed incremental population.

6.54 The PBAC acknowledged various sensitivity analyses put forward in the July 2021 dapagliflozin pre-PBAC response (incorporating a price reduction and other adjustments) but considered that the analyses did not overcome the fundamental issues with the model structure that reduced confidence in the resulting ICERs. The PBAC remained concerned that the model structure was not robust but considered, at the time, that dapagliflozin would be cost-effective at the reduced price, comparable to other treatments for chronic conditions (para 7.8, dapagliflozin PSD, July 2021 PBAC meeting with September 2021 Addendum and November 2021 Addendum).

6.55 Key drivers of the economic model are summarised in Table 11, below.

Table 11: Key drivers of the model

Description	Method/Value	Impact
Time horizon	The resubmission nominated a 15-year time horizon based on the time horizon in the dapagliflozin July 2021 submission. The ESC previously considered that the 15-year time horizon in the dapagliflozin submission was too short and resulted in delayed ESKD and death events being converted into avoided events. The ESC considered that dapagliflozin may delay time to ESKD and therefore any impacts would be delayed rather than avoided (para 6.45, dapagliflozin PSD, July 2021 PBAC meeting). The model estimated that 8.7% of SC patients and 28.1% of empagliflozin plus SC patients remain alive at 15 years, and any differences in the incidence of ESKD and deaths at this timepoint were translated into avoided events.	High, favours empagliflozin

Description	Method/Value	Impact
Transitions to ESKD	Transition probabilities from CKD to ESKD were informed by time to ESKD data from the incremental subgroup of EMPA-KIDNEY. The applicability of the incremental subgroup in the trial to the PBS population is uncertain given the heterogeneity in baseline risk across the various subpopulations, with available data suggesting a substantially higher proportion of patients with milder disease in the Australian setting. The modelled risks of ESKD were heavily weighted by patients with eGFR <45 mL/min/1.73 m^2 which are unlikely to be applicable to patients with milder disease. It is also unclear whether treatment effects associated with empagliflozin would be affected by differences in other characteristics such as age, sex, presence of comorbidities and UACR levels, with significant treatment interactions for diabetes status and UACR levels in the trial.	High, favours empagliflozin
ESKD survival	Transition probabilities from ESKD to death were informed by time to ESKD data from the incremental subgroup of EMPA-KIDNEY. The resubmission assumed a fixed distribution of patients receiving different treatment modalities (conservative care, dialysis, transplant) and transitions between these treatments were not modelled. Trial-based ESKD survival estimates were informed by sparse data over a limited observation period, in which few patients had received a kidney transplant. Extrapolation of these data are unlikely to reflect longer term survival; or reflect Australian clinical practice given differences in the use of ESKD treatment modalities. Modelled overall survival in patients with ESKD in the standard care arm was substantially lower than Australian survival estimates among patients on renal replacement therapy. Further, the resubmission modelled a survival advantage for empagliflozin in patients with ESKD; which was inadequately supported by the available data that showed no statistically significant difference between empagliflozin and standard care.	Uncertain
Treatment persistence	The resubmission adjusted the cost of empagliflozin over time based on a Gompertz extrapolation of treatment persistence estimates from the EMPA-KIDNEY trial. The use of the Gompertz function was inadequately justified as it assumed an accelerating probability of treatment discontinuation over time which may not be representative of long-term persistence to treatment. The model also inappropriately assumed ongoing treatment benefit despite few patients remaining on treatment over time (see Figure 3, below).	High, favours empagliflozin
ESKD costs	The fixed distribution of ESKD treatment modalities is unlikely to reflect the relative exposure to each treatment modality as patients are likely to transition between treatments over time (e.g. conservative care may be used to temporarily delay the use of renal replacement therapies, dialysis may be used until a transplant becomes available). The validity of ESKD treatment costs in the model could not be determined due to insufficient documentation in the cited sources. The inclusion of separately estimated ESKD monitoring costs was inadequately justified and may lead to duplication of costs already captured in ESKD treatment costs.	Variable due to ESKD survival assumptions

Source: Constructed during the evaluation
Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; SC, standard care; UACR, urinary albumin creatinine ratio

6.56 Table 12 summarises the incremental costs for health resource items used in the model.

Table 12: Health care resource items: disaggregated summary of cost impacts

Type of resource item (discounted)	Empagliflozin + SC	SC	Incremental cost
Treatment costs	$[redacted]	$988	$[redacted]
- Empagliflozin	$[redacted]	$0	$[redacted]
- Standard care	$1,228	$988	$240
Monitoring	$5,250	$4,318	$933
- CKD monitoring	$4,535	$3,640	$894
- ESKD monitoring	$716	$677	$38
ESKD treatment	$79,712	$77,073	$2,639
- Conservative care	$161	$153	$7
- Dialysis (initial)	$3,396	$4,554	-$1,158
- Dialysis (ongoing)	$74,972	$70,944	$4,027
- Kidney transplant (initial)	$603	$808	-$205
- Kidney transplant (ongoing)	$580	$613	-$32
Terminal care	$13,501	$17,648	-$4,147
Total costs	**$[redacted]**	**$100,026**	**$[redacted]**

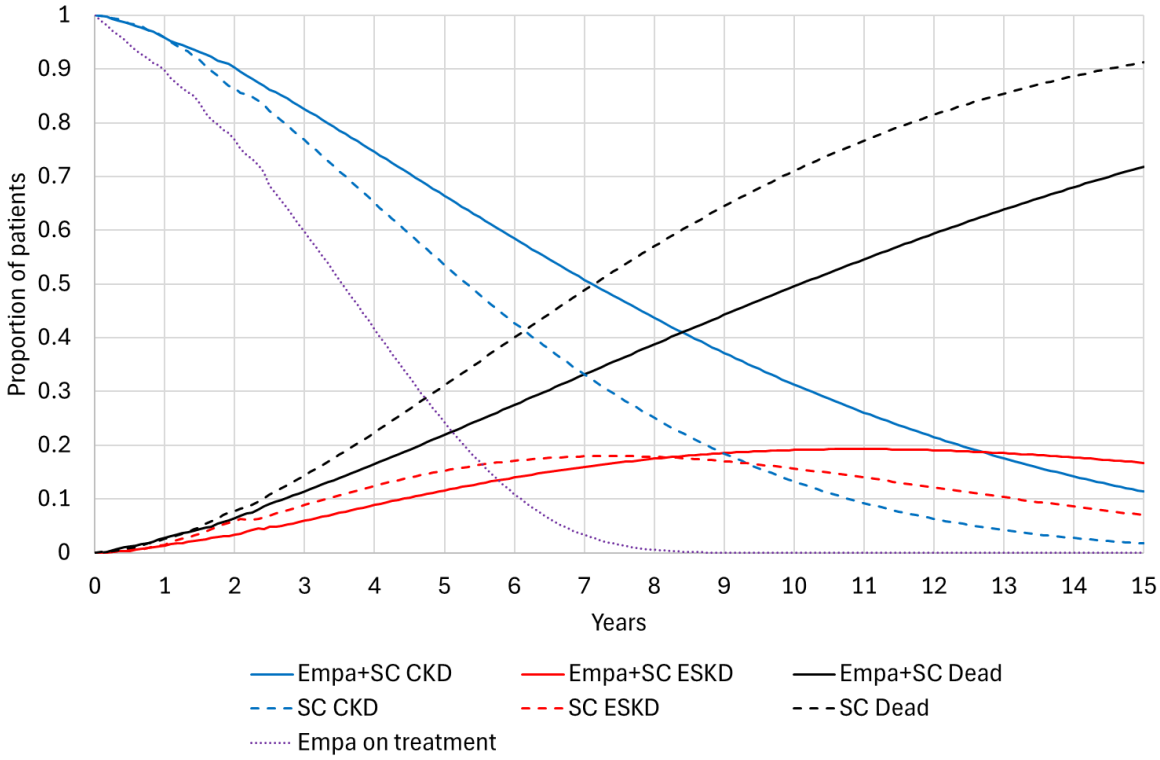
Source: Table 3.25, p338 and the Section 3 economic model of the resubmission
Abbreviations: CKD, chronic kidney disease; ESKD, end-stage kidney disease; SC, standard care

6.57 In the model, fewer patients progressed to ESKD in the empagliflozin plus SC arm compared to the SC arm. However, there was an increase in time spent in the ESKD health state in the empagliflozin plus SC arm compared to the SC arm due to differences in survival in the ESKD health state.

6.58 Consequently, the difference in total cost between treatment arms was driven by a net increase in ESKD treatment costs (predominantly ongoing dialysis costs partially offset by initial dialysis costs) and additional costs of empagliflozin in the empagliflozin plus SC arm. These costs were partially offset by reduced terminal care costs in the empagliflozin plus SC arm.

6.59 Figure 3 presents the model trace of empagliflozin plus SC versus SC alone.

Figure 3: Model trace for health state membership



Source: Section 3 economic model of the resubmission
Abbreviations: CKD, chronic kidney disease; Empa, empagliflozin; ESKD, end-stage kidney disease; SC, standard care

6.60 Over the 15-year time horizon, more patients in the empagliflozin plus SC arm remained alive compared to the SC arm. At 15 years, 28.1% of patients in the empagliflozin plus SC arm were alive compared to 8.7% in the SC arm. Modelled survival benefits in the empagliflozin plus SC arm compared to the SC arm were predominantly due to a greater proportion of patients remaining in the CKD state due to avoidance of ESKD and ESKD transitions to death.

6.61 The traces show a declining proportion of patients remaining on empagliflozin treatment over time, with approximately 10% on treatment at 6 years in the model. The assumption that treatment benefits continue to persist despite few patients remaining on therapy over time may not be reasonable, with no data to support residual treatment benefits with empagliflozin. The impact of this assumption could not be tested in sensitivity analyses as modelled time on treatment was only used to reduce treatment costs, with no impact on treatment effects.

6.62 The results of the stepped economic evaluation are summarised in Table 13.

Table 13: Results of the stepped economic evaluation for the incremental population (base case)

Step and component	Empagliflozin + SC	SC	Increment
Step 1: ITT population characteristics, time horizon 31 months, modelled transition probabilities, include treatment costs (empagliflozin and standard care), 5% discounting for costs and outcomes			
Costs	$[redacted]	$454	$[redacted]
Life years	2.3849	2.3738	0.0111
		Incremental cost per life year gained	$[redacted] [1]
Step 2: Extrapolate to 15 years			
Costs	$[redacted]	$988	$[redacted]
Life years	7.5246	6.2292	1.2955
		Incremental cost per life year gained	$[redacted] [2]
Step 3: Add disease monitoring costs, ESKD treatment costs and terminal care costs			
Costs	$[redacted]	$100,026	$[redacted]
Life years	7.5246	6.2292	1.2955
		Incremental cost per life year gained	$[redacted] [2]
Step 4: Add CKD and ESKD health state utilities			
Costs	$[redacted]	$100,026	$[redacted]
QALYs	5.8230	4.8122	1.0108
		Incremental cost per QALY gained	$[redacted] [2]

Source: Table 3.24, p337 of the resubmission

Abbreviations: CKD, chronic kidney disease; ESKD, end-stage kidney disease; ITT, intent to treat; QALY, quality-adjusted life year; SOC, standard care

The redacted values correspond to the following ranges:

[1] *$135,000 to < $155,000*

[2] *$0 to < $5,000*

6.63 Treatment with empagliflozin plus SC was associated with an incremental cost per QALY gained of $0 to < $5,000 compared to SC alone in the modelled PBS incremental population with chronic kidney disease.

6.64 The cost-effectiveness of patients with varying baseline disease severity (e.g. moderate, high and very high risk) could not be determined as the modelled population was based on the overall incremental population in the trial. The data suggest potential differences between the composition of the incremental population in the trial and in clinical practice, with a higher proportion of patients with milder CKD in clinical practice compared to the trial.

6.65 During the evaluation, it was noted that 99.7% of incremental QALYs are accrued in the extrapolated period beyond 2 years. Incremental costs are accrued in the extrapolated period due to improved survival of patients in the ESKD state in the empagliflozin plus SC arm compared to the SC arm.

6.66 The results of key sensitivity analyses are summarised in Table 14.

Table 14: Sensitivity analyses

Analysis	Incremental cost	Incremental QALY	ICER	Change from base case ICER
Base case	$[redacted]	**1.0108**	$[redacted] [1]	-
Discount rate (base case 5% for benefits and costs)				
3.5% discount rate	$[redacted]	1.1506	$[redacted] [1]	+[redacted]%
0% discount rate	$[redacted]	1.5814	$[redacted] [2]	+[redacted]%
Time horizon (base case 15 years)				
30 years	$[redacted]	1.3961	$[redacted] [3]	+[redacted]%
20 years	$[redacted]	1.2666	$[redacted] [2]	+[redacted]%
10 years	-$[redacted]	0.5523	Dominant	-
Transition probabilities from CKD to ESKD (base case extrapolation using independent Weibull functions)				
Independent exponential functions	$[redacted]	0.8539	$[redacted] [1]	-[redacted]%
Independent Gompertz functions	$[redacted]	1.0468	$[redacted] [4]	+[redacted]%
Independent lognormal functions	-$[redacted]	0.9144	Dominant	-
Independent loglogistic functions	$[redacted]	0.9665	$[redacted] [1]	[redacted]%
Independent generalised gamma functions	$[redacted]	0.8246	$[redacted] [4]	+[redacted]%
Weibull function for empagliflozin + SC, lognormal function for SC (best statistical fit)	$[redacted]	0.8234	$[redacted] [5]	+[redacted]%
Transition probabilities from CKD to death (base case extrapolation using independent Weibull functions)				
Independent exponential functions	-$[redacted]	0.8983	Dominant	-
Independent Gompertz functions	$[redacted]	0.8824	$[redacted] [2]	+[redacted]%
Independent lognormal functions	-$[redacted]	0.9857	Dominant	-
Independent loglogistic functions	$[redacted]	0.9920	$[redacted] [1]	-[redacted]%
Independent generalised gamma functions	$[redacted]	1.3346	$[redacted] [1]	+[redacted]%
No difference between arms (both based on modelled survival in the empagliflozin + SC arm)	-$[redacted]	0.6952	Dominant	-
No difference between arms (both based on modelled survival in the SC arm)	-$[redacted]	0.5508	Dominant	-
Transition probabilities from ESKD to death (base case extrapolation using independent exponential functions)				
Independent Weibull functions	-$[redacted]	0.9181	Dominant	-
Independent Gompertz functions	-$[redacted]	0.5796	Dominant	-
Independent lognormal functions	-$[redacted]	0.8197	Dominant	-
Independent loglogistic functions	-$[redacted]	0.8515	Dominant	-
Independent generalised gamma functions	-$[redacted]	0.6355	Dominant	-
Weibull function for empagliflozin + SC, lognormal function for SC (best statistical fit)	-$[redacted]	0.7605	Dominant	-
No difference between arms (both based on modelled survival in the empagliflozin + SC arm)	-$[redacted]	0.5323	Dominant	-
No difference between arms (both based on modelled survival in the SC arm)	-$[redacted]	0.6925	Dominant	-
ESKD treatment costs based on fixed distribution across treatment modalities (base case 14.8% conservative care, 81.7% dialysis, 3.5% kidney transplant based on Morton 2011; costs derived from the Deloitte Access Economics February 2023 report and other publications)				
Conservative management 50% (AIHW 2016; incidence); distribution between dialysis (37.7%) and transplant (12.3%) based on 2023 ANZDATA incidence estimates	-$[redacted]	1.0108	Dominant	-
EMPA-KIDNEY trial (0% conservative care, 94.6% dialysis, 5.4% transplant)	$[redacted]	1.0108	$[redacted] [1]	+[redacted]%

Analysis	Incremental cost	Incremental QALY	ICER	Change from base case ICER
Double conservative management (30%), distribution between dialysis (37.4%) and transplant (32.6%) based on 2023 ANZDATA prevalence estimates.	-$[redacted]	1.0108	Dominant	-
Remove all ESKD treatment costs	-$[redacted]	1.0108	Dominant	-
Terminal care costs (base case $26,112 based on Reeve 2018)				
$4,568 based on NHCDC 2021-22 AN-SNAP 5BT1	$[redacted]	1.0108	$[redacted] [2]	+[redacted]%

Source: Table 3.27, p341 and the Section 3 economic model of the resubmission

Abbreviations: AIHW, Australian Institute of Health and Welfare; AN-SNAP, Australian National Subacute and Non-Acute Patient classification; ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; CI, confidence interval; CKD, chronic kidney disease; ESKD, end-stage kidney disease; ICER, incremental cost-effectiveness ratio; ITT, intent to treat; QALY, quality adjusted life year; UACR, urinary albumin creatinine ratio

The redacted values correspond to the following ranges:

[1] *$0 to < $5,000*

[2] *$5,000 to < $15,000*

[3] *$15,000 to < $25,000*

[4] *$45,000 to < $55,000*

[5] *$35,000 to < $45,000*

6.67 The model was most sensitive to transition probabilities from CKD to ESKD, time horizon, transition probabilities from CKD to death, the discount rate and terminal care costs.

6.68 The removal of modelled survival benefits associated with empagliflozin in the CKD and ESKD health states (independent of avoidance of ESKD) resulted in a dominant result for empagliflozin plus SC compared to SC alone. The results appear counterintuitive but are primarily due to ongoing ESKD costs in the empagliflozin plus SC arm that shift from an increased cost in the base case (due to improved survival in the ESKD state) to a cost offset when survival probabilities are the same as the SC arm.

6.69 Due to structural limitations, the impact of other potentially more important parameters could not be adequately tested in sensitivity analyses. This included variations in baseline risk of disease progression and treatment effects, empagliflozin treatment persistence and the circumstances of use of treatment modalities (conservative care, dialysis, transplant) in end-stage kidney disease.

6.70 The resubmission also presented scenario analyses based on alternative populations (ITT, UACR <200 mg/g, UACR ≥200 mg/g) used to inform transition probabilities between health states. The analyses did not appear informative as the ITT population includes patients who are eligible under the existing CKD listing (overlap population) while the UACR <200 mg/g only partially covers the requested incremental population (eGFR 25 to <45 mL/min/1.73 m^2 with UACR <200 mg/g and potentially eGFR 20 to <25 mL/min/1.73 m^2).

6.71 The ESC noted that the economic issues were largely driven by a lack of relevant clinical data. Although the resubmission updated the model based on the simplified structure used for dapagliflozin in July 2021, the PBAC had previously considered the

model structure overly simple and not robust (paragraph 7.8, dapagliflozin (chronic kidney disease), PSD, July 2021 PBAC meeting). Although the ICER remains consistently low in sensitivity analyses, the ESC had little confidence in the base case result, given concerns regarding the robustness of the model because of its structure.

6.72 The pre-PBAC response presented univariate analyses using a revised lower price for empagliflozin (1 April 2025 AEMP $39.02) noting the ICER remains consistently low even after significantly reducing the treatment benefit of empagliflozin, assuming no difference in risk of death in patients with CKD and ESKD, increasing treatment duration and reducing ESKD monitoring and end-of-life costs. The sensitivity analyses aligning the duration of treatment with empagliflozin with the time to developing ESKD and reducing end-of-life cost to the estimate suggested during the evaluation increased the ICER to $0 to < $5,000 and $5,000 to < $15,000/QALY, respectively. The sensitivity analysis with risk of CKD to ESKD in the empagliflozin arm converging to placebo plus SC starting at month 38 and full convergence at 180 months, resulted in an ICER of $5,000 to < $15,000/QALY gained.

Drug cost/patient/year

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)*	-	$58.85	$58.85
Adherence	Patient-reported, at least 94% took most of the study medication [a]	100%	90%
No. scripts per year	-	12.1750 [b]	10.9575 [b]
Cost per year	-	$716.53 [c]	$644.85 [c]
Proportion of patients on treatment (persistence)	After a mean follow-up of 23.9 months, 76.8% of patients in the empagliflozin arm remained on treatment [d]	Year 1: 89.7% [e] Year 2: 76.8% [e] Year 3: 59.7% [e] Year 4: 41.6% [e] Year 5: 24.3% [e] Year 6: 10.9% [e]	Not estimated

Source: Constructed during the evaluation
Abbreviation: DPMQ, dispensed price maximum quantity
[a] Based on the EMPA-KIDNEY ITT population
[b] Calculated as the estimated number of scripts required per year (365.25 ÷ 30) adjusted for treatment adherence
[c] Calculated based on proposed DPMQ and number of scripts per year
[d] Based on time to treatment discontinuation for empagliflozin in the incremental subgroup of the EMPA-KIDNEY trial
e Based on modelled treatment persistence unadjusted for deaths
*nb – the table is not updated with the revised DPMQ from 1 April 2025, $55.41

6.73 The estimated empagliflozin drug costs differed between the economic analysis and financial estimates due to differences in assumptions relating to treatment compliance (adherence and persistence).

Estimated PBS usage & financial implications

6.74 This resubmission was not considered by DUSC. The original submission was considered by DUSC at the November 2023 meeting.

6.75 The resubmission used an epidemiological approach to estimate the utilisation and financial impacts associated with the PBS listing of empagliflozin for the treatment of adults with CKD in the incremental population not currently eligible to receive dapagliflozin or empagliflozin on the PBS, using the same methodology and assumptions as the November 2023 submission, updated or adjusted as required.

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

Table 16: Key inputs for financial estimates

Data	Value applied and source	Comment
Proportion of Australian adults with CKD	11%; based on AIHW 'Chronic Kidney Disease: Australian facts', updated 17 June 2024.	Unchanged from the November 2023 submission. DUSC previously considered that there is significant uncertainty in the current prevalence of CKD in the Australian population (para 6.94, empagliflozin PSD, November 2023 PBAC meeting). The pre-PBAC response noted the latest ABS NHMS 2022-2024 data suggesting that 14.2% of Australians have indicators of CKD. The pre-PBAC response suggested that the use of the 11% estimate of CKD prevalence would have led to an underestimation of the proposed PBS incremental population and the resultant financial estimates.
Adults likely to be diagnosed with CKD	65% in Year 1; increasing by 5% each year to 90% in Year 6. PBAC previously suggested the proportion of CKD that is diagnosed should be 50% in Year 1 (2022) of dapagliflozin estimates, and increase 5% per year (para 15.4, dapagliflozin PSD, November 2021 PBAC meeting). Accordingly, the proportion of CKD diagnosed would be 65% in 2025 (Year 1) of estimates.	Updated from the November 2023 submission (60-85%). DUSC previously considered the proportion of CKD likely to be diagnosed was overestimated, and that the assumption of a linear increase over 6 years was uncertain (para 6.94, empagliflozin PSD, November 2023 PBAC meeting). Estimates in the resubmission are higher than in the November 2023 submission, and still assume a linear increase over time.
Proportion of all diagnosed CKD patients in the incremental population	13.52%; based on the average of values derived from the 2011-2012 ABS National Health Measures Survey (NHMS; 8.4%) and Neuen 2023 (18.7%). NHMS data reported the proportions of patients with eligible eGFR levels, excluding patients with CKD stage 5. The proportions of patients with micro and macroalbuminuria were derived from the overall population in the absence of more granular data. Proportions of patients with eGFR >5000 mg/g were not reported. Neuen 2023 presents the results of an Australian retrospective cohort analysis of patients matching the EMPA-KIDNEY incremental population in terms of eGFR and UACR (based on selected patients captured in the MedicineInsight database).	Increased from 8.4% in the November 2023 submission (based on NHMS data only). DUSC previously considered that the NHMS data was uncertain and potentially an underestimate (Table 16, empagliflozin PSD, November 2023 PBAC meeting). The averaging of the values derived from Neuen 2023 the NHMS data was not reliable, given DUSC's concerns with the NHMS data. Estimates from Neuen 2023 may not be reliable, given the reliance on selected MedicineInsight data, and the exclusion of a large proportion of patients with eGFR 25 to <45 mL/min/1.73 m^2 without a UACR measurement.
Proportion of patients who are receiving stable ACEi/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).	Unchanged from the November 2023 submission. 82.1% of patients in the EMPA-KIDNEY incremental subgroup, and 58.1% of patients in the incremental subgroup in Neuen 2023 were receiving ACEi/ARBs.
Proportion of patients without T2DM	50%; based on PBAC feedback on the November 2021 dapagliflozin submission (Table 23, dapagliflozin PSD, November 2021 PBAC meeting), and ANZDATA Registry data, where close to 50% of Australian patients in 2019 had Type 2 diabetes on initiation of renal replacement therapy.	Adjusted from the November 2023 submission, in which an additional 27.9% of T2DM patients ineligible for SGLT2 inhibitors due to HbA1c <7% was assumed. 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.

Data	Value applied and source	Comment
		49.0% of patients in the EMPA-KIDNEY incremental subgroup, and 42.6% of patients in the incremental subgroup in Neuen 2023 had T2DM.
Proportion of patients with CKD without heart failure	87.49%; based on the complement of the proportion of patients in the EMPA-KIDNEY incremental subgroup (12.51%).	90% was used in the November 2023 submission, based on the complement of the proportion of patients with heart failure in the overall EMPA-KIDNEY population (10%). 10.0% of patients in the incremental subgroup in Neuen 2023 had heart failure.
Uptake rate	[redacted]% in Year 1; increasing by [redacted]% per year to [redacted]% in Years 5 and 6; assumed.	Increased from [redacted]-[redacted]% in the November 2023 empagliflozin submission, which DUSC considered to be an underestimate. Assumed uptake rates are highly uncertain.
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.	This was considered uncertain, with no data presented in support of the estimated adherence rate in the incremental CKD population.

Source: Table 4.1, pp346-347 of the submission.

Abbreviations: ABS, Australian Bureau of Statistics; AIHW, Australian Institute of Health and Welfare; CKD, chronic kidney disease; HFrEF, heart failure with reduced ejection fraction; PSD, Public Summary Document; RRT, renal replacement therapy; SGLT2, sodium glucose cotransport-2; T2DM, type 2 diabetes mellitus; UACR, urine albumin-creatinine ratio

6.77 Table 17 summarises the estimated utilisation and net cost to the PBS/RPBS of listing empagliflozin on the PBS/RPBS for the incremental CKD population. Costs were based on 30 day dispensing and markups, incorporating the April 2025 price reduction (DPMQ $55.41). The pre-PBAC response noted applying the lower 1 April 2025 price resulted in net savings to the PBS of $0 to < $10 million in Year 1 increasing to $0 to < $10 million in Year 6, which translates to total cumulative savings of $10 million to < $20 million to the PBS over the six-year period.

Table 17: Estimated use and financial implications of listing empagliflozin for the incremental CKD population

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Number of eligible patients	[redacted]10	[redacted]10	[redacted]11	[redacted]12	[redacted]12	[redacted]13
November 2023 submission eligible population	[redacted]9	[redacted]9	[redacted]10	[redacted]11	[redacted]11	[redacted]12
Number of patients treated	[redacted]8	[redacted]9	[redacted]10	[redacted]11	[redacted]12	[redacted]12
November 2023 submission treated patients	[redacted]6	[redacted]7	[redacted]8	[redacted]9	[redacted]10	[redacted]11
Number of scripts dispensed[a]	[redacted]15	[redacted]16	[redacted]17	[redacted]18	[redacted]20	[redacted]20
November 2023 submission total scripts	[redacted]13	[redacted]15	[redacted]16	[redacted]17	[redacted]18	[redacted]19
Net cost to PBS/RPBS (less co-payment)	$[redacted]2	$[redacted]3	$[redacted]3	$[redacted]4	$[redacted]4	$[redacted]5
Net cost to PBS/RPBS (less co-payment) – new DPMQ $55.41	$[redacted]2	$[redacted]2	$[redacted]3	$[redacted]3	$[redacted]4	$[redacted]4
November 2023 submission net PBS/RPBS cost	$[redacted]1	$[redacted]2	$[redacted]2	$[redacted]3	$[redacted]3	$[redacted]4

Source: Tables 4.18-4.20, p366 of the resubmission.

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARBs, angiotensin II receptor blocker; CKD, chronic kidney disease; DPMQ, dispensed price for maximum quantity; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme; SGLT2i, sodium glucose cotransport-2 inhibitor; T2D, type 2 diabetes.
[a] Scripts per year calculated as < 500 scripts per year [redacted], adjusted for [redacted]% adherence [redacted].
Note: The number of scripts per year and total cost were based on 30 day dispensing, and markups at 1 April 2025.
Note: For November 2023 estimates, the number of scripts per year and total cost was recalculated during the evaluation to correspond to 30 day dispensing, and the total cost was based on the DPMQ with markups at 1 July 2023.
The redacted values correspond to the following ranges:
[1] *$10 million to < $20 million*
[2] *$20 million to < $30 million*
[3] *$30 million to < $40 million*
[4] *$40 million to < $50 million*
[5] *$50 million to < $60 million*
[6] *30,000 to < 40,000*
[7] *40,000 to < 50,000*
[8] *50,000 to < 60,000*
[9] *60,000 to < 70,000*
[10] *70,000 to < 80,000*
[11] *80,000 to < 90,000*
[12] *90,000 to < 100,000*
[13] *100,000 to < 200,000*
[14] *400,000 to < 500,000*
[15] *500,000 to < 600,000*
[16] *600,000 to < 700,000*
[17] *700,000 to < 800,000*
[18] *800,000 to < 900,000*
[19] *900,000 to < 1,000,000*
[20] *1,000,000 to < 2,000,000*

6.78 The estimated net cost to the PBS/RPBS of listing empagliflozin for the treatment of CKD in the incremental population (based on 30 day dispensing and 1 April 2025 markups) was $20 million to < $30 million in Year 1, increasing to $40 million to < $50 million in Year 6, an estimated cumulative net cost of $200 million to < $300 million in the first six years of listing. The estimated net cost to the PBS/RPBS of listing empagliflozin for the treatment of CKD in the incremental population was larger than estimated in the November 2023 submission (estimated cumulative net cost of $100 million to < $200 million in the first six years of listing).

6.79 The estimated cost to the PBS/RPBS was considered uncertain due to the following reasons:

- The proportion of Australian adults with CKD was unchanged in the resubmission. DUSC previously considered that there was significant uncertainty in the current prevalence of CKD in the Australian population; and 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 (para 6.94, empagliflozin PSD, November 2023 PBAC meeting).
- DUSC previously considered the estimated proportions of patients 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 (Table 16, empagliflozin PSD,

November 2023 PBAC meeting). The resubmission assumed higher proportions of patients diagnosed over time, based on a [redacted]% linear increase.

- The proportion of the CKD patients in the incremental subgroup was updated in the resubmission, based on the average of the estimate used previously (based on the 2011-2012 ABS National Health Measures Survey) and the estimate from Neuen 2023 (based on a retrospective cohort analysis of patients captured in the MedicineInsight database representing the EMPA-KIDNEY incremental population in terms of eGFR and UACR). DUSC previously considered that the estimate based on NHMS data was uncertain and potentially an underestimate (Table 16, empagliflozin PSD, November 2023 PBAC meeting). Estimates from Neuen 2023 may not be reliable, given the reliance on selected MedicineInsight data, and the exclusion of a large proportion of patients with eGFR 25 to <45 mL/min/1.73 m^2 without a UACR measurement.
- Uptake rates, previously considered by DUSC to be an underestimate, were increased in the resubmission, but are based on assumption, and highly uncertain.

Quality Use of Medicines

6.80 The sponsor stated that comprehensive education will be provided to health care professionals and patients, and that activities to support quality use of medicines and post-marketing surveillance for empagliflozin are ongoing.

Financial Management – Risk Sharing Arrangements

6.81 The resubmission stated that there is a current risk-sharing arrangement (RSA) for the SGLT2 inhibitor class of medications (empagliflozin and dapagliflozin) across two separate indications: chronic heart failure with left ventricular ejection fraction ≤40%; and chronic kidney disease.

6.82 The resubmission proposed an increase in the current RSA caps to accommodate the addition of the incremental CKD population. The proposed increase was based on the estimated financial implications of listing empagliflozin for the incremental population, added to the current RSA caps. The sponsor proposed that the higher caps be applied to empagliflozin only, and that the current caps for dapagliflozin should remain unchanged. The resubmission argued that the clinical and cost-effectiveness of dapagliflozin in the incremental population has not been demonstrated, therefore it is not appropriate to extend the increased caps to dapagliflozin.

6.83 The sponsor claimed that adjustments to the reimbursement formula for dapagliflozin would be required given the proposed changes would affect the total Commonwealth Payment and market share estimates in the class-based RSA. The sponsor claimed that this would ensure that the sponsor for dapagliflozin would not be unfairly disadvantaged from the increased overall market size for CKD. The adjustments are

reliant on the estimated use of empagliflozin for the CKD overlap population based on a [redacted] split across the overlap and incremental populations, respectively.

6.84 The risk share proposal adjustment for the Deed for dapagliflozin was outlined in Section 5 of the submission. The proposed changes to caps in the empagliflozin RSA are summarised in Table 18.

Table 18: Proposed changes to the current RSA for empagliflozin

	Indication	Year 4 (2025)	Year 5 (2026)	Source/calculation
Current RSA caps	HFrEF	[redacted]		
	CKD (overlap)			
	Total			
Proposed increase in RSA caps	CKD (incremental)			
Proposed RSA caps	HFrEF			
	CKD (overlap + incremental)			
	Total			

Source: Table 5.2, p376 and Table 5.6, p380 of the resubmission
Abbreviations: CKD, chronic kidney disease; HFrEF, heart failure with reduced ejection fraction; RSA, risk-sharing arrangement

6.85 The PBAC considered that an increase to the existing shared RSA caps would be appropriate to account for the incremental population. However, it was noted that the implementation arrangements of the joint subsidisation caps with other parties to the RSA was not a matter for the empagliflozin sponsor and would be administered by the Department per its usual practices.

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

7 PBAC Outcome

7.1 The PBAC recommended the extension of the current Authority Required (STREAMLINED) listing of empagliflozin for chronic kidney disease (CKD) to include the proposed incremental population that was previously not recommended by the PBAC at the November 2023 meeting. The PBAC was satisfied that empagliflozin provides, for some patients in the proposed incremental population, a significant improvement in efficacy over standard care. The PBAC's recommendation for the extended listing was based on its assessment that the cost-effectiveness of empagliflozin in the proposed incremental population would be acceptable at the existing PBS price, which was recently reduced, and which mitigated the significant uncertainties identified in the economic model. The PBAC also recommended an adjustment to the existing risk sharing arrangement to account for the extended population for empagliflozin.

7.2 The PBAC noted the increasing prevalence of CKD in the Australian population and the higher burden of disease in Aboriginal and Torres Strait Islander people, indicating the clinical need for effective intervention to preserve residual kidney function for patients at risk of significant kidney disease progression. The PBAC noted the support

from health professionals, Kidney Health Australia and the Australian Diabetes Society for broader access to SGLT2 inhibitors in CKD, particularly for patients with eGFR 20 - 45 mL/min/1.73 m^2, regardless of UACR levels. The PBAC noted that the risk of CKD progression in the incremental population ranged from moderately increased risk to very high risk, similar to the population currently eligible for PBS treatment with an SGLT2 inhibitor. The PBAC also considered the clinical evidence of a benefit in the incremental population was adequately demonstrated in this resubmission and comparable to the population currently eligible for PBS treatment.

7.3 The PBAC supported amendments to the existing empagliflozin restriction to allow treatment beyond the current overlap population (eGFR 25 to 75 mL/min/1.73 m^2 with UACR 200 to 5,000 mg/g) to include the aggregated incremental subgroups in the key clinical trial (EMPA-KIDNEY):

- eGFR 20 to <25 mL/min/1.73 m^2, regardless of UACR.
- eGFR 25 to <45 mL/min/1.73 m^2 with UACR <200 mg/g.
- eGFR 25 to 75 mL/min/1.73 m^2 with UACR >5,000 mg/g.
- eGFR >75 to 90 mL/min/1.73 m^2 with UACR ≥200 mg/g.

7.4 The PBAC considered the narrower TGA indication for dapagliflozin and advised that there should be no flow-on to dapagliflozin as a result of the extended listing of empagliflozin. However, given that international guidelines consider benefits of SGLT2 inhibitors as a class effect, the PBAC advised further consideration of a flow-on to dapagliflozin would be welcome with updated available evidence.

7.5 The PBAC reaffirmed its previous acceptance of placebo (add-on to standard care) as the appropriate comparator in the incremental population (see paragraph 5.2).

7.6 The PBAC noted the resubmission re-presented previously considered results of the EMPA-KIDNEY trial overall ITT population, and *post hoc* subgroup analyses of the EMPA-KIDNEY trial for the currently reimbursed overlap population, and the proposed PBS incremental population. In addition, the resubmission presented new *post hoc* analyses of the EMPA-KIDNEY trial not previously considered by the PBAC for primary and key secondary outcomes by baseline albuminuria (UACR <200 mg/g and UACR ≥200 mg/g). The PBAC also noted the recent publication of a two-year open-label follow-up study of EMPA-KIDNEY (Herrington et al, 2025) and the publication of the prespecified secondary analysis of the EMPA-KIDNEY trial examining the annualised rate of decline of kidney function (eGFR slope) (Staplin et al, 2024). The PBAC felt that this additional data was supportive of a clinical benefit of empagliflozin in the incremental population.

7.7 The PBAC noted the significant benefit in the ITT population for the primary composite outcome of CKD progression or CV death (HR = 0.72 (0.64, 0.82)) and time to first CKD

progression (HR = 0.71 (0.62, 0.81)), with minimal differences in the significant results for the overlap and incremental subgroups (see Table 6). The PBAC considered the clinical benefit in the incremental subgroup was clinically meaningful and reflected that it was comparable to the results previously accepted in the overlap subgroup when non-inferiority to dapagliflozin was accepted.

7.8 The PBAC acknowledged that the magnitude of absolute benefit would vary given the heterogeneous nature of CKD populations and was mindful of its previous concern regarding efficacy in patients with lower albuminuria. The PBAC was reassured by the two-year follow-up data and analyses of the eGFR slope, which signalled a continuing benefit for patients on empagliflozin beyond the end of the randomised trial phase, regardless of albuminuria level (see paragraphs 6.19, 6.21 and 6.22). The PBAC also noted Australian and international guidelines consistently supported the inclusion of SGLT2 inhibitors for CKD in the incremental population.

7.9 The PBAC considered empagliflozin was effective in both the incremental and overlap populations, noting the magnitude of benefit would be slightly less, but still clinically meaningful, in the UACR <200mg/g subgroup in the long-term. The PBAC noted most patients accessing PBS treatment would have a higher UACR. Overall, the PBAC was satisfied that, despite the remaining uncertainty in the absolute magnitude of benefit, the claim of superior effectiveness in the incremental population compared to placebo plus standard care was reasonable.

7.10 The PBAC reaffirmed its previous consideration that a claim of non-inferior comparative safety for empagliflozin versus placebo plus standard care in the incremental population was reasonable (para 6.50, empagliflozin PSD, November 2023 PBAC meeting).

7.11 The PBAC noted the resubmission presented a revised simplified model structure aligned with that used in the dapagliflozin submission in response to the PBAC's view that the economic analysis presented in the November 2023 empagliflozin submission, using microsimulation, was overly complex. The resubmission model combined different CKD stages into a single CKD health state (stage 2-4) and single ESKD health state (conservative care, dialysis, transplant) and death. The PBAC noted the ESC's concerns regarding the resubmission model, particularly that:

- modelled risks of events were heavily weighted by patients with eGFR <45 mL/min/1.73m^2 which may not be applicable to patients with milder disease
- estimates of ESKD treatment duration, persistence and discontinuation and the associated costs and ongoing treatment benefits may not be appropriate

- while many of the sensitivity analyses resulted in the ICER being dominant, the estimated ICER was highly dependent on the choice of extrapolation function and thus uncertain
- 99.7% of the incremental QALYs was accrued during the extrapolation period

The PBAC considered that the issues with the revised economic model in the resubmission were mostly driven by deficiencies in clinical data.

7.12 An additional sensitivity analysis presented in the pre-PBAC response adjusted risk of CKD to ESKD to be the same as placebo plus standard of care and starting at month 38 and full convergence at 180 months and resulted in an ICER of $5,000 to < $15,000 which was considered by PBAC to be more informative given the limited long-term evidence but still likely optimistic. The PBAC noted that, while multiple issues with the economic model created uncertainty, the ICER in the various sensitivity analyses were consistently low. The PBAC remained concerned that the model structure was not robust, however, at the recently reduced price, the PBAC was confident that the ICER would be in an acceptable range, comparable to other treatments for chronic conditions.

7.13 PBAC noted the estimated eligible population and financial implications had increased since the November 2023 submission. The PBAC noted that estimated uptake rates, previously considered to have been underestimated by DUSC, were increased in the resubmission. However, PBAC noted that in practice, uptake of medications for CKD is generally low and advised that experience with uptake in the overlap population may be a reasonable indicator of uptake in the incremental population. The PBAC also noted the reduced price from 1 April 2025 resulted in a $10 million to < $20 million lower cost to the PBS over the six-year period, compared to the cost based on previous prices (see paragraph 6.77).

7.14 The PBAC considered that an increase to the current risk sharing arrangement expenditure caps was appropriate and should be based on [redacted].

7.15 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and* Vaccines – *Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for empagliflozin:

a) The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy over alternative therapies, based on the uncertain magnitude of benefit in the incremental subgroup beyond the 24-month EMPA-KIDNEY trial period;

b) The treatment is not expected to address a high and urgent unmet clinical need, given this is a request for the extension of an existing listing in a heterogeneous

patient population;

c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

7.16 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Amend existing listing as follows:

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
EMPAGLIFLOZIN					
empagliflozin 10 mg tablet, 30	14092Q	1	30	5	Jardiance
Category / Program: ☒ GENERAL - General Schedule (Code GE)					
Prescriber type: ☒Medical Practitioners ☒Nurse practitioners					
Restriction type: ☒Authority Required (Streamlined) [new/existing code]					
Administrative Advice: **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 Practitioners.					
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Episodicity: Chronic					
Severity: n/a					
Condition: Kidney disease					
Indication: Chronic kidney disease					
Treatment Phase: n/a					
Clinical criteria:					
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					
AND					
Clinical criteria:					
Patient must have an estimated glomerular filtration rate of between 20 to 90 mL/min/1.73 m2 inclusive prior to initiating treatment with this drug					
AND					
Clinical criteria:					
Patient must have a urinary albumin to creatinine ratio of at least 200 mg/g (22.6mg/mmol) if the patient has an estimated glomerular filtration rate of between 45 to 90 mL/min/1.73 m^2 inclusive prior to initiating treatment with this drug					
AND					

Clinical criteria:
Patient must discontinue treatment with this drug prior to initiating renal replacement therapy, defined as dialysis or kidney transplant
AND
Clinical criteria:
Patient must not be receiving treatment with another sodium-glucose co-transporter 2 (SGLT2) inhibitor
AND
Clinical criteria:
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
Prescribing Instructions: 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.