

An addendum to these PSDs have been included at the end of the document.

6.03 DAPAGLIFLOZIN, Tablet 10 mg, Forxiga[®], AstraZeneca Pty Ltd

1 Purpose of submission

- 1.1 The Category 1 submission requested an Authority Required (Streamlined) General Schedule listing of dapagliflozin for the treatment of chronic kidney disease (CKD).
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis of dapagliflozin plus standard of care (SOC) versus SOC alone.
- 1.3 A concurrent resubmission for dapagliflozin for the treatment of symptomatic heart failure with reduced ejection fraction (HFrEF) was considered at the July 2021 PBAC meeting (item 7.01 refers). The submission acknowledged that there was substantial overlap between eligible populations targeted by the existing type 2 diabetes mellitus (T2DM), and proposed HFrEF and CKD PBS listings.

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

Component	Description
Population	Patients with CKD with an eGFR of ≥ 25 to ≤ 75 mL/min/1.73 m ² , UACR of ≥ 200 and ≤ 5000 mg/g, and stable for at least 4 weeks on a maximum tolerated dose of an ACEI or ARB (unless contraindicated)
Intervention	Dapagliflozin 10 mg once daily, plus SOC comprised of at least an ACEI or ARB (unless contraindicated)
Comparator	Placebo, plus SOC comprised of at least an ACEI or ARB (unless contraindicated)
Outcomes	Primary composite outcome: time to the first occurrence of $\geq 50\%$ sustained decline in eGFR, end-stage kidney disease (defined as sustained eGFR < 15 mL/min/1.73m ² , or chronic dialysis treatment, or receiving a renal transplant), cardiovascular death or renal death. Secondary composite outcomes: time to the first event of $\geq 50\%$ sustained decline in eGFR, ESKD, or renal death; time to first event of cardiovascular death or hospitalisation for heart failure; death by any cause. Safety.
Clinical claim	Dapagliflozin added to SOC demonstrates superior efficacy and non-inferior safety compared with SOC alone in patients with CKD

Source: Table 1.1.1, p.41 of the submission.

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; ESKD, end stage kidney disease; eGFR, estimated glomerular filtration rate; SOC, standard of care; UACR, urinary albumin to creatinine ratio

2 Background

Registration status

- 2.1 **TGA status at time of PBAC consideration:** This submission for dapagliflozin was submitted under the TGA/PBAC parallel process and was granted priority review

status for this indication on 13 November 2020. At the time of the evaluation and the ESC meeting, no TGA documents were available. At the time of the PBAC meeting, the Clinical Evaluation Report and the TGA Delegate's Overview were available.

2.2 The proposed TGA indication for dapagliflozin is:

Dapagliflozin is indicated in adults for the treatment of chronic kidney disease.

2.3 Dapagliflozin is also TGA registered for use in adults with T2DM:

- As monotherapy as an adjunct to diet and exercise in patients for whom metformin is otherwise indicated but was not tolerated.
- As initial combination therapy with metformin, as an adjunct to diet and exercise, to improve glycaemic control when diet and exercise have failed to provide adequate glycaemic control and there are poor prospects for response to metformin monotherapy (for example, high initial haemoglobin A1c [HbA1c] levels).
- In combination with other anti-hyperglycaemic agents to improve glycaemic control, when these together with diet and exercise, do not provide adequate glycaemic control.
- For the treatment of patients with established cardiovascular disease or risk factors for cardiovascular disease to reduce the risk of hospitalisation for heart failure.

2.4 In addition, dapagliflozin was listed on the Australian Register of Therapeutic Goods for the treatment of adults with symptomatic HF_{rEF} as an adjunct to standard of care therapy in November 2020.

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

3 Requested listing

3.1 In the table below, further additions proposed by the Secretariat and some additions by the ESC are added in italics and suggested deletions are crossed out with strikethrough. The PBAC noted that this table does not reflect all ESC advice outlined in the text below, nor the PBAC's additional recommendations as outlined in section 7 *PBAC Outcome*.

Public Summary Document – July 2021 PBAC Meeting with September 2021 Addendum
and November 2021 Addendum

MEDICINAL PRODUCT medicinal product pack	Max. qty packs	Max. qty units	No. of Rpts	Available brands
DAPAGLIFLOZIN				
dapagliflozin 10 mg tablet, 28	1	28	5	Forxiga
Restriction Summary [new] / Treatment of Concept: [new]				
Category / Program: GENERAL – General Schedule (Code GE)				
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners				
Restriction type: <input checked="" type="checkbox"/> Authority Required – Streamlined [new code]				
Indication: Chronic kidney disease				
Treatment Phase: Initial/continuing [blank]				
Clinical criteria:				
Patient must have an estimated glomerular filtration rate of ≥ 25 and ≤ 75 mL/min/1.73m ² between 25 and 75 mL/min/1.73 m ² inclusive, to substantiate the diagnosis of kidney disease, prior to initiating treatment with this drug,				
AND				
Clinical criteria:				
Patient must have a urinary albumin to creatinine ratio of ≥ 200 and ≤ 5000 mg/g between 200 and 5000 mg/g inclusive, to substantiate the diagnosis of kidney disease, prior to initiating treatment with this drug,				
AND				
Clinical criteria:				
Patient must not progress to end-stage renal disease defined as an estimated glomerular filtration rate (eGFR) of less than 15 mL/min/1.73 m ² while on this drug.				
AND				
Clinical criteria:				
Patient must be stable on the maximum tolerated dose of an angiotensin converting enzyme inhibitor OR an angiotensin II receptor blocker for at least 4 weeks prior to initiating therapy with dapagliflozin, unless medically contraindicated,				
AND				
Clinical criteria:				
Patient must receive dapagliflozin in combination with an angiotensin converting enzyme inhibitor OR an angiotensin II receptor blocker unless medically contraindicated, Patient must receive treatment in combination with the maximum tolerated dose of an ACE inhibitor; or Patient must receive treatment in combination with the maximum tolerated dose of an angiotensin II antagonist				
AND				
Clinical criteria:				
Patient must not be receiving treatment with another sodium-glucose co-transporter 2 (SGLT2) inhibitor.				
Prescribing Instructions:				
Patient must be stabilised on either (i) an ACE inhibitor or (ii) an angiotensin II antagonist for a period of 4 weeks prior to initiation of combination therapy with this drug.				
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.				

3.2 The requested dispensed price for dapagliflozin for CKD was \$ [REDACTED] (DPMQ per pack of 28 tablets).

- 3.3 Consistent with the requirements of the *National Health Act 1953* to have a single published list price per pharmaceutical item, the sponsor requested a revised published price for dapagliflozin to reflect proportional use across T2DM (\$56.85), CKD (\$██████) and HFrEF (\$██████) indications. A proposed weighted price was not provided in the submission, but was included in the Pre-Sub-Committee Response (PSCR) (\$██████ for CKD and T2DM, \$██████ for CKD and T2DM and HFrEF). The ESC had been concerned that the weightings were highly uncertain and that patients currently using PBS-subsidised dapagliflozin for T2DM were already experiencing the associated benefits in heart failure and kidney function at the T2DM DPMQ. The pre-PBAC response offered a revised DPMQ of \$██████, to align with the ██████ price. At the time of the PBAC meeting, the ██████ price was \$██████.
- 3.4 The requested restriction was narrower than the proposed TGA indication in that it limited initial eligibility to patients meeting specific clinical criteria (i.e. eGFR ≥ 25 and ≤ 75 mL/min/1.73m², UACR ≥ 200 and ≤ 5000 mg/g), who are treated with a maximum tolerated dose of an ACEI or ARB, unless medically contraindicated. The requested restriction did not differentiate UACR criteria by sex, and may include different severity of disease between males and females. The ESC advised that UACR should be expressed both in mg/g and mg/mmol as both are reported in pathology laboratories in Australia.
- 3.5 While the restriction was consistent with the inclusion criteria of the key clinical trial and the clinical definition of CKD in terms of decline in eGFR, UACR and continuing treatment with an ACEI or ARB as a key component of SOC (KHA 2020), the clinical criteria omitted the requirement for patients to exhibit symptoms of kidney disease for ≥ 3 months.
- 3.6 The restriction did not exclude patients with reversible acute kidney injury, CKD with transient reductions in kidney function, or specific causes of CKD excluded from the key clinical trial; i.e. polycystic kidney disease, autoimmune kidney disease such as systemic lupus erythematosus, and anti-neutrophil cytoplasmic antibody (ANCA) related vasculitis (there is no evidence to support the use of dapagliflozin in these patients). The ESC advised that the restriction should specifically state that the patient must have sustained evidence of CKD for three months at the time of initiation of dapagliflozin, with exclusion of reversible causes and exclusion of autosomal polycystic kidney disease, T1DM and kidney disease secondary to vasculitic aetiology. The PBAC noted that patients with a history of organ transplantation were also excluded from the key trial.
- 3.7 The requested restriction did not include stopping criteria, so patients may continue treatment with PBS subsidised dapagliflozin for CKD after onset of end-stage kidney disease (ESKD) or initiation of dialysis. The Secretariat had proposed a criterion of “Patient must not progress to end-stage renal disease defined as an estimated glomerular filtration rate (eGFR) of less than 15 mL/min/1.73 m² while on this drug.” The ESC advised the PBAC to consider whether a stopping rule (for eGFR

<25 mL/min/1.73 m² or commencement on renal replacement therapy) should be included in the restriction. The pre-PBAC response (p1) noted that patients with eGFR <25 mL/min/1.73 m² were ineligible to initiate therapy in the trial. However, it explained that stopping therapy was left to clinician judgement and around 30% of patients received treatment, and continued to receive benefits, when their eGFR was less than 25 mL/min/1.73 m². The pre-PBAC response also noted that 2% (n=43) of patients remained on therapy during dialysis and 0.1% (n=2) remained on treatment following kidney transplant. The pre-PBAC response argued that the PBS restriction should align with the trial criteria (i.e. treatment should be stopped according to clinician judgement), however it acknowledged the limited evidence for patients on renal replacement therapy.

- 3.8 The PBAC was also asked to consider whether ACEI/ARB-intolerant or contraindicated patients should still be eligible for dapagliflozin (as proposed in the submission), noting that the proportion of patients in the clinical trial who were not receiving an ACEI/ARB was very low. The Secretariat had suggested removing elements of the proposed criteria that permitted use of dapagliflozin where ACEI/ARB use was “medically contraindicated”.
- 3.9 The submission acknowledged that the requested restriction included the use of dapagliflozin in patients with an eGFR <45 mL/min/1.73 m². The approved dapagliflozin Product Information (PI) at the time of the PBAC meeting (p2) stated that, “FORXIGA should not be used to improve glycaemic control in the treatment of diabetes in patients for whom the estimated glomerular filtration rate (eGFR) is persistently below 45 mL/min/1.73 m².” An amendment to the PI warning was requested as part of the regulatory approval for dapagliflozin for CKD, based on evidence from the DAPA-CKD trial, stating that the glucose lowering effect of dapagliflozin may be reduced in patients with an eGFR of <45 mL/min/1.73 m². The sponsor proposed to remove the requirement for additional monitoring of renal function prior to or after initiation of dapagliflozin in patients with diabetes mellitus with impaired kidney function, but to include a recommendation that if eGFR falls below 45 mL/min/1.73 m², additional glucose lowering treatment should be considered in patients with diabetes mellitus.
- 3.10 The TGA delegate commented that under the PI “Special warnings and precautions for use”:
- Renal function monitoring recommendation guidance should be reinstated.
 - The following warnings should be included:
 - “FORXIGA is not recommended for use to improve glycaemic control in adults with type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m². FORXIGA is likely to be ineffective in this setting based upon its mechanism of action.”
 - “FORXIGA is not recommended for the treatment of chronic kidney disease in patients with polycystic kidney disease, lupus nephritis or ANCA-associated

vasculitis or patients requiring or with a recent history of immunosuppressive therapy for kidney disease. FORXIGA is not expected to be effective in these populations.”

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 disease and risk factors (e.g. diabetes, hypertension, cardiovascular disease, obesity, prior acute kidney injury, family history of kidney disease, smoking, age > 60 years) (Kidney Health Australia (KHA) 2020). Mild and moderate CKD is frequently asymptomatic, and diagnosis missed or delayed until the onset of severe kidney disease.
- 4.2 CKD is defined as having one or both of the following criteria, irrespective of underlying cause (KHA 2020):
- an eGFR of <60 mL/min/1.73 m² that is present for three months or more with or without evidence of kidney damage; or
 - evidence of kidney damage with or without a decrease in eGFR, present for three months or more; i.e. albuminuria, haematuria, structural abnormalities, pathological abnormalities.
- 4.3 Progression of CKD is described in terms of declining glomerular filtration rate (CKD stage 1-5) and abnormal albuminuria/proteinuria, and may be asymptomatic up to severe disease (CKD stage 4) or ESKD.
- 4.4 Approximately one in three Australian adults are at risk of developing CKD, one in ten have early signs of disease and up to 1.7 million may be living with undiagnosed CKD (Australian Bureau of Statistics (ABS) 2011–12 Australian Health Survey). The prevalence of CKD has remained stable over time, is similar between females and males, with the incidence, prevalence and severity of disease increasing with age, and progressing rapidly from 75 years.
- 4.5 CKD may progress to ESKD (CKD 5: eGFR < 15 mL/min/1.73 m², renal disease requiring dialysis) or renal death. The most common causes of CKD resulting in ESKD in Australia are diabetes (38%), hypertension (13%), glomerulonephritis (13%) and polycystic kidney disease (6.6%). The age-standardised incidence of treated ESKD increased from 6 per 100,000 in 1989 to 11 per 100,000 in 2018. This increase was greater for males (15 per 100,000), than for females (8 per 100,000). Indigenous Australians are 2 times more likely to experience CKD compared to non-Indigenous Australians, 9 times more likely to progress to treated ESKD and 11 times more likely to be treated with dialysis.

- 4.6 The population targeted in the submission (adult patients with CKD, eGFR ≥ 25 and ≤ 75 mL/min/1.73 m² and UACR ≥ 200 and ≤ 5000 mg/g, receiving stabilised treatment with a maximum tolerated dose of an ACEI or ARB, unless contraindicated), was broad in terms of decline in kidney function, and consistent with the goals of early detection and disease management of CKD in the clinical guidelines (KHA 2020; KDIGO 2020).
- 4.7 Dapagliflozin is a selective sodium-glucose co transporter 2 (SGLT2) inhibitor. While the pharmacological action of dapagliflozin in CKD has not been established, the submission suggested that inhibition of SGLT2 may activate tubuloglomerular feedback and lower intraglomerular pressure, preserving renal function and delaying kidney disease progression. The submission suggested that this mechanism of action is independent of the glucose lowering action of dapagliflozin in T2DM and the impact of ACEI or ARB therapies on intraglomerular pressure.
- 4.8 The clinical management algorithm positioned dapagliflozin as a pharmacological addition to standard of care (SOC) in CKD, administered concurrently with an ACEI or ARB (unless contraindicated).

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

5 Comparator

- 5.1 The submission nominated SOC as the main comparator. The submission noted that there are no other medications for the treatment of CKD listed on the PBS, and that ACEIs and ARBs (unless contraindicated) are the only pharmacological interventions commonly recommended for the treatment CKD in clinical guidelines.
- 5.2 The submission acknowledged that CKD frequently co-exists with other health conditions such as diabetes and heart failure, and individual patients may also receive other medications related to co-morbidities, or treatments to prevent or manage complications of CKD such as anaemia and renal bone disease.
- 5.3 During the evaluation it was noted that EMPA-KIDNEY study, a randomised double-blind placebo-controlled trial of empagliflozin versus placebo (N \approx 6,000) in the treatment of CKD with or without diabetes is underway, with an expected completion date of October 2022. Given the completion date and lack of study details or interim results, empagliflozin was not considered further in the Commentary.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the high clinical need for new therapeutic options in the treatment of CKD, and claimed that the DAPA-CKD trial population and outcomes would be applicable to the Australian setting. The

clinician also discussed the circumstances under which dapagliflozin for CKD might be used. In particular, they emphasised that patients whose eGFR progressed below 25 mL/min/1.73 m² while on treatment would continue to receive benefits as they had done in the trial. However, the clinician acknowledged there was little evidence to support continued treatment after commencement of renal replacement therapy, and suggested that these patients should cease treatment. The clinician also emphasised that patients who are ACEI/ARB-contra-indicated would benefit from access to dapagliflozin, noting that the mechanism of benefit of SGLT2 inhibition is not dependent on the background blockade of the renin-angiotensin system, and that the clinical need for effective therapies like dapagliflozin is in fact higher in this patient group as they are unable to be treated with existing standard of care. In addition, the clinician highlighted that the DAPA-CKD outcomes were likely to be the same regardless of whether patients have CKD only, or also have HFREF and/or T2DM.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (9), health care professionals (18) and organisations (4) via the Consumer Comments facility on the PBS website. Comments were received from the Centre for Community-Driven Research, Diabetes Australia, Kidney Health Australia, and the National Aboriginal Community Controlled Health Organisation. The comments discussed a range of benefits of treatment with dapagliflozin for CKD including improvements in quality of life, a reduction in (co)morbidity and mortality, and delaying the need for renal replacement therapy. The comments described dapagliflozin as well tolerated, with a known safety profile from its long-term use in T2DM. The comments also described the clinical needs of specific populations including Aboriginal and Torres Strait Islander patients and those with T2DM. Dapagliflozin was described as a significant therapeutic advance in the treatment of CKD.

Clinical trial

6.3 The submission was based on one head-to-head randomised controlled trial comparing dapagliflozin plus SOC to SOC alone (DAPA-CKD).

6.4 Details of the trial are provided in the table below.

Table 2: Trials presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
DAPA-CKD	A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney (Clinical Study Report) Heerspink HJL et al. Dapagliflozin in patients with chronic kidney disease Wheeler DC et al. The dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD) trial: baseline characteristics	28 September 2020 <i>New England Journal of Medicine</i> 2020; 383:1436-1446 <i>Nephrology Dialysis Transplant</i> 2020; 35(10):1700-1711

Source: Table 2.2.1, p.57 of the submission

6.5 The key features of the DAPA-CKD trial are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in model
DAPA-CKD	4,304	R, DB, PC, MC 24 mths	Low	Adults with CKD and eGFR ≥ 25 – ≤ 75 mL/min/1.73 m ² ; and UACR 200-5,000 mg/g; treated with maximum tolerated dose of ACEI/ARB	Primary composite outcome: $\geq 50\%$ decline in eGFR, ESKD, CV death, or renal death; other composite outcomes and safety	<i>Post hoc</i> survival analyses informed transitions from CKD to ESKD, CKD to death, ESKD to death

Source: Constructed during the evaluation

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; SOC, standard of care; UACR, urinary albumin to creatinine ratio.

- 6.6 The DAPA-CKD trial was an international, multicentre trial, conducted in the Asian (31%), European (28%), North American (19%), and South American (21%) geographic regions. No Australian sites were included in the trial.
- 6.7 The DAPA-CKD trial was designed with an intended duration of 45 months and estimated mean treatment duration of 33 months. On 26 March 2020, the trial was terminated early on the basis of overwhelming efficacy following 509 primary outcome events. Duration of treatment and follow up was truncated (median duration 28.5 months). Given the short study duration, the DAPA-CKD trial data may not be sufficiently mature to inform long-term outcomes relevant to the use of dapagliflozin in CKD.
- 6.8 The DAPA-CKD trial included patients regardless of T2DM and HFrEF status, but excluded patients with type 1 diabetes mellitus (T1DM). The trial also excluded patients with autosomal dominant or autosomal recessive polycystic kidney disease, lupus nephritis, anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis, history of severe cardiovascular disease (e.g. NYHA class IV heart failure, myocardial infarction or coronary revascularisation), organ transplant, or recent treatment with cytotoxic or immunosuppressive medicines.
- 6.9 The median age of patients was 64 years, and the trial comprised more males (67%) than females (33%), with demographic and disease characteristics distributed similarly in both treatment arms. Most patients reported baseline CKD stage 3 disease (median 41.0-42.0 mL/min/1.73 m²), with a median UACR of 950 mg/g.
- 6.10 Baseline characteristics were generally well matched between treatment arms of the DAPA-CKD trial. However, there was a smaller proportion of patients with CKD stage 4 at baseline in the dapagliflozin plus SOC treatment arm (13.6%) compared to SOC alone (15.4%), with increased baseline risk of ESKD.
- 6.11 The proportion of patients with T2DM was monitored at randomisation, and allocation between treatment arms supervised to ensure a minimum of 30% of T2DM patients in each arm. The proportion of patients with CKD and T2DM in the trial

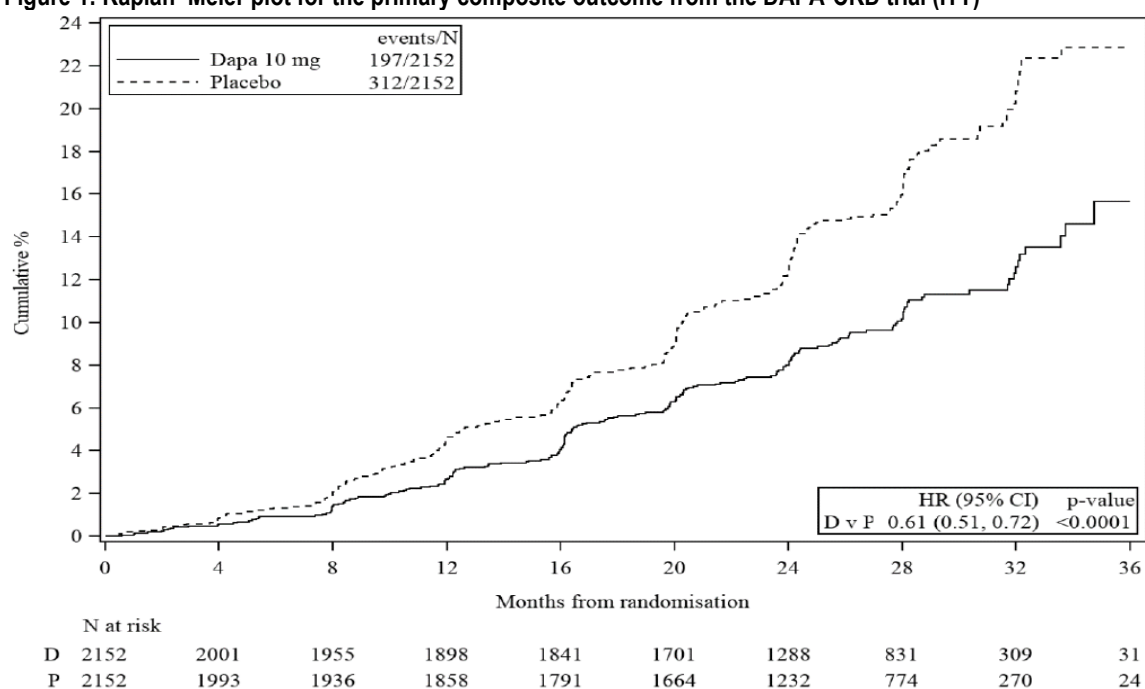
(67.4%) was substantially higher than the 30% minimum. The ESC noted that no reason for this very high proportion of patients with T2DM was provided by the submission. The ESC felt that this had the potential to affect the baseline risk of the eligible PBS population.

6.12 Baseline use of diabetes medicines in patients with T2DM was similar between treatment arms, with the most commonly reported glycaemic control medicines being insulin (55.4%), metformin (43.0%), sulfonylureas (26.8%) and DPP-4 inhibitors (25.7%), and remained similar between treatment arms during the trial. The high proportion of patients with T2DM reporting treatment with insulin was not adequately explained, and may have impacted the incidence of adverse events related to glycaemic control.

Comparative effectiveness

6.13 Figure 1 and Table 4 present the results of the DAPA-CKD trial primary composite outcome (time to first event of $\geq 50\%$ decline in kidney function, ESKD or death from renal or cardiovascular causes) based on the pre-specified hierarchical testing sequence.

Figure 1: Kaplan–Meier plot for the primary composite outcome from the DAPA-CKD trial (ITT)



Source: Figure 2.5.1, p.80 of the submission

D or Dapa, dapagliflozin; CI, confidence interval; ESKD, end-stage kidney disease; HR, hazard ratio; ITT, intention-to-treat; P, placebo

Table 4: Results for the primary composite outcome from the DAPA-CKD trial (ITT)

Outcome	Dapagliflozin + SOC N=2,152	SOC N=2,152	Hazard ratio (95% CI)
Primary composite outcome, n (%)	197 (9.2%)	312 (14.5%)	0.61 (0.51, 0.72)
Median duration of treatment, mean (range)	27.3 months (0-39.0)	27.0 months (0-38.8)	-
Primary outcome components (exploratory outcomes), n (%)			
≥50% decline in eGFR	112 (5.2%)	201 (9.3%)	0.53 (0.42, 0.67)
ESKD	109 (5.1%)	161 (7.5%)	0.64 (0.50, 0.82)
Sustained eGFR <15 mL/min/1.73 m ²	84 (3.9%)	120 (5.6%)	0.67 (0.51, 0.88)
Long-term dialysis (adjudicated)	68 (3.2%)	99 (4.6%)	0.66 (0.48, 0.90)
Kidney transplant	3 (0.1%)	8 (0.4%)	NR
Renal death (adjudicated)	2 (<0.1%)	6 (0.3%)	NR
Cardiovascular death (adjudicated)	65 (3.0%)	80 (3.7%)	0.81 (0.58, 1.12)

Source: Table 2.5.1, p.79 of the submission

eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; NR, not reported; SOC, standard of care

- 6.14 Treatment with dapagliflozin plus SOC was associated with a statistically significant improvement in the primary composite endpoint of time to ≥50% decline in kidney function, ESKD or death from renal or cardiovascular causes compared to SOC alone (HR 0.61: 95% CI [0.51, 0.72]). The key drivers of the primary composite outcome were time to a ≥50% decline in eGFR or ESKD.
- 6.15 Results from exploratory analyses of the individual components of the primary endpoint showed nominal benefits associated with dapagliflozin for decline in eGFR and ESKD. The numbers of events of renal death and kidney transplant were very small, and the differences between treatment arms could not be statistically estimated.
- 6.16 Table 5 summarises the results of the key secondary outcomes of the DAPA-CKD trial included in the hierarchical testing sequence following demonstration of statistical significance for the primary outcome. Dapagliflozin plus SOC was associated with a statistically significant improvement in terms of each secondary outcome, compared to SOC alone.

Table 5: Results for the secondary outcomes from the DAPA-CKD trial (ITT)

Outcome	Dapagliflozin plus SOC N=2,152	SOC N=2,152	Hazard ratio (95% CI)
Secondary outcomes, n (%)			
Time to first event of ≥50% decline in eGFR, ESKD, or renal death, n (%)	142 (6.6%)	243 (11.3%)	0.56 (0.45, 0.68)
Time to first event of cardiovascular death, or hospitalisation for HF, n (%)	100 (4.6%)	138 (6.4%)	0.71 (0.55, 0.92)
Death from any cause, n (%)	101 (4.7%)	146 (6.8%)	0.69 (0.53, 0.88)

Source: Table 2.5.1, p.79 of the submission

eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HF, heart failure; ITT, intention-to-treat; SOC, standard of care

- 6.17 EQ-5D-5L utility scores remained similar over time in both treatment arms. Similar results were observed for the KDQOL-36, with no clinically relevant changes compared to baseline observed for either treatment arm.

Pre-specified subgroup analyses

- 6.18 The benefit of dapagliflozin in the primary composite outcome was generally consistent across the pre-specified subgroups. Tests for treatment effect interaction indicated a significant interaction by baseline systolic blood pressure, with dapagliflozin being associated with a smaller magnitude of effect in patients with systolic blood pressure >130 mmHg. The PSCR (p1) reiterated that dapagliflozin plus SOC remained significantly more efficacious than SOC alone regardless of baseline systolic blood pressure. In addition, it noted that 64.7% of Australians with diabetes, CKD or cardiovascular disease are estimated to have blood pressure over 130/80 mmHg (Hoare et al, 2018), which is comparable to the 64.2% of patients in the DAPA-CKD trial with a systolic blood pressure of >130 mmHg. Therefore, the PSCR argued, the trial results in the subgroups analysed were likely to be applicable for the Australian population.
- 6.19 The submission noted the results of the primary outcome were similar for the subgroups with an eGFR of ≥ 45 or < 45 mL/min/1.73m², and suggested that the treatment effect of dapagliflozin in patients with CKD is independent of its glycaemic effect. Differences in event rates between complementary subgroups in the comparator arm of the DAPA-CKD trial (SOC alone) suggested differences in baseline risk in the eGFR (< 30 26.3%; ≥ 30 12.4% OR < 45 17.4%; ≥ 45 10.5%), as well as the UACR (≤ 1000 7.5%; > 1000 22.1%) and T2DM status (yes 15.8%; no 11.8%) subgroups.
- 6.20 Differences in event rates between complementary subgroups in the comparator arm of the DAPA-CKD trial were also observed by region (Asia 10.6%; Europe 14.3%; North America 16.8%; Latin/South America 18.4%), suggesting health system effects, which may limit the applicability of results of the trial to the Australian setting.
- 6.21 Results of the subgroup analyses for the key secondary composite outcomes were generally consistent across subgroups. However, there were significant treatment effect interactions in the $\geq 50\%$ eGFR decline, ESKD or renal death composite outcome for baseline systolic blood pressure and the cardiovascular death or heart failure hospitalisation composite outcome for sex (dapagliflozin was associated with a smaller magnitude of effect in males).
- 6.22 For the key secondary composite outcomes, there were differences in event rates between complementary subgroups in the comparator arm suggesting differences in baseline risk by eGFR and UACR category, diabetes status and region.

Post hoc analyses

- 6.23 Table 6 summarises the results of the *post hoc* analyses in the DAPA-CKD trial (ITT). Results of the *post hoc* analyses were used to inform transition probabilities in the economic model.

Table 6: Results of the *post hoc* analyses* in the DAPA-CKD trial (ITT)

Outcome	Dapagliflozin + SOC (N)	SOC (N)	Overall ITT Hazard ratio (95% CI)
Primary composite outcome	2,152	2,152	0.61 (0.51, 0.72) ^a
Time to ESKD excluding deaths prior to ESKD	2,067	2,033	0.63 (0.50, 0.81)
Time to death from any cause in patients not progressing to ESKD	2,043	1,991	0.69 (0.52, 0.91)
Time from ESKD to death from any cause	109	161	0.86 (0.46, 1.63)

Source: Table 2.6.1, p.92 of the submission; KMcurves_Section261.docx, Attachment 2.5 of the submission

CI, confidence interval; ESKD, end-stage kidney disease; ITT, intention-to-treat

^a From Table 2.5.1, p79 of the submission. Shown above in Table 4: Results for the primary composite outcome from the DAPA-CKD trial (ITT), and provided again here for comparative purposes.

* Note that the results presented in Table 6 are derived from *ad-hoc/post-hoc* analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plans for DAPA-CKD. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

- 6.24 In the *post hoc* analyses, treatment with dapagliflozin plus SOC was associated with nominal improvements in time to ESKD (excluding deaths prior to ESKD), and time to death from any cause in patients not progressing to ESKD, compared to SOC alone. Results for time from ESKD to death from any cause showed no difference between dapagliflozin plus SOC compared to SOC alone.
- 6.25 Given the overlapping populations between T2DM, HFrEF and CKD, the submission also conducted *post hoc* subgroup analyses to inform the effectiveness and cost-effectiveness of dapagliflozin in patients not eligible for PBS-subsidised dapagliflozin for T2DM or HFrEF.
- 6.26 Patient demographic and disease characteristics for the CKD only subgroup (and complement subgroup) were not reported. Subgroup sample sizes reported for the Kaplan-Meier plots could not be verified, and the numbers of patients in the CKD only subgroup (excluding patients with T2DM or HFrEF) exceeded the numbers of patients in the DAPA-CKD trial reporting no T2DM at baseline; i.e. DAPA-CKD dapagliflozin + SOC = 696, SOC = 700; CKD only subgroup dapagliflozin + SOC = 1,359, SOC = 1,363. This was not addressed in the PSCR or pre-PBAC response.
- 6.27 Table 7 summarises the results of *post hoc* subgroup analyses in the population with CKD only (without T2DM or HFrEF), and its complement subgroup. Results of the CKD only subgroup were used to inform a scenario analysis in the economic evaluation.

Table 7: Results of the *post hoc* subgroup analyses* in the DAPA-CKD trial (CKD only subgroup)

Outcome	Dapagliflozin + SOC (N)	SOC (N)	Hazard ratio (95% CI)
CKD only subgroup			
Primary composite outcome	1,359	1,363	0.67 (0.54, 0.83)
Time to ESKD excluding deaths prior to ESKD	1,323	1,312	0.70 (0.54, 0.92)
Time to death from any cause in patients not progressing to ESKD	1,265	1,237	0.69 (0.45, 1.06)
Time from ESKD to death from any cause	94	126	1.10 (0.53, 2.26)
Complement subgroup			
Primary composite outcome	793	789	0.51 (0.57, 0.70)
Time to ESKD excluding deaths prior to ESKD	744	721	0.41 (0.22, 0.75)
Time to death from any cause in patients not progressing to ESKD	778	754	0.69 (0.47, 0.99)
Time from ESKD to death from any cause	15	35	0.47 (0.08, 2.70)

Source: KMcurves_Section261.docx, Attachment 2.5; and Table 1, p.2, Figures 1-8, in CKD_only_population.docx, Attachment 3.2 of the submission

CI, confidence interval; ESKD, end-stage kidney disease; ITT, intention-to-treat

* Note that the results presented in Table 6 are derived from *ad-hoc/post-hoc* analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plans for DAPA-CKD. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

- 6.28 The submission noted that the results of the subgroup analysis of the CKD only population for the primary composite outcome and time to ESKD excluding deaths prior to ESKD nominally favoured dapagliflozin plus SOC compared to SOC alone. Time to death from any cause in patients not progressing to ESKD and time from ESKD to death did not reach nominal significance in the CKD only population. Lack of significance in time from ESKD to death from any cause was likely related to small sample size.
- 6.29 Patient demographic and disease characteristics, and treatment effect interaction were not reported for the CKD only subgroups. Given insufficient data were presented in the submission to assess the validity of the CKD only subgroup, the results of the subgroup analyses should be interpreted with caution. The PSCR (p2) noted that the CKD only subgroup analysis was a supportive analysis intended to help demonstrate the efficacy and cost-effectiveness of dapagliflozin in the population of patients who are not already eligible for PBS-subsidised treatment with this medication for T2DM and who will not be eligible under the proposed HFrEF indication should the PBAC recommend it (item 7.01 refers).

Comparative harms

6.30 Table 8 summarises the results of safety outcomes for the DAPA-HF trial.

Table 8: Summary of key adverse events in the DAPA-CKD trial (Safety Analysis Set)

Events n (%)	Dapagliflozin + SOC	SOC
N	2,149	2,149
Key adverse events		
Any serious adverse event	633 (29.5%)	729 (33.9%)
Adverse event leading to discontinuation	118 (5.5%)	123 (5.7%)
Adverse event leading to dose interruption	272 (12.7%)	268 (12.5%)
Adverse event leading to dose reduction	39 (1.8%)	31 (1.4%)
Adverse event leading to death ^a	106 (4.9%)	159 (7.4%)
Adverse event related to treatment	275 (12.8%)	222 (10.3%)
Major hypoglycaemic event ^b	14 (0.7%)	28 (1.3%)
Symptoms of volume depletion	120 (5.6%)	84 (3.9%)
Deaths (on treatment)	67 (3.1%)	85 (4.0%)
Serious adverse events with frequency of ≥ 0.5%		
Any serious adverse event	594 (27.6%)	674 (31.4%)
Acute kidney injury	36 (1.7%)	44 (2.0%)
Pneumonia	36 (1.7%)	58 (2.7%)
Heart failure	35 (1.6%)	48 (2.2%)
Acute myocardial infarction	28 (1.3%)	38 (1.8%)
Ischaemic stroke	21 (1.0%)	22 (1.0%)
Urinary tract infection	20 (0.9%)	13 (0.6%)
Cellulitis	14 (0.7%)	15 (0.7%)
Angina unstable	12 (0.6%)	22 (1.0%)
Transient ischaemic attack	11 (0.5%)	8 (0.4%)
Cardiac failure congestive	10 (0.5%)	16 (0.7%)
Cerebrovascular accident	10 (0.5%)	8 (0.4%)
Myocardial infarction	10 (0.5%)	5 (0.2%)
Osteomyelitis	10 (0.5%)	10 (0.5%)
Prostate cancer	10 (0.5%)	5 (0.2%)
Hypoglycaemia	9 (0.4%)	17 (0.8%)
Sepsis	9 (0.4%)	14 (0.7%)
Atrial fibrillation	6 (0.3%)	17 (0.8%)
Hyperkalaemia	6 (0.3%)	11 (0.5%)
Hyperglycaemia	5 (0.2%)	15 (0.7%)

Source: Table 2.5.5, p.89 of the submission; Table 28, p.120 of the DAPA-CKD CSR, Attachment 2.3 of the submission
SOC, standard of care

^a Includes death on and off treatment.

^b Investigator defined as symptoms of severe impairment in consciousness or behaviour, needing external assistance and intervention to treat hypoglycaemia, with prompt recovery of acute symptoms.

6.31 Patients treated with dapagliflozin plus SOC reported fewer serious adverse events compared to SOC alone (27.6% vs 31.4%, respectively). However, larger proportions of patients treated with dapagliflozin reported adverse events related to treatment (12.8% vs 10.3%) and symptoms of volume depletion (5.6% vs 3.9%) compared to placebo.

6.32 The most commonly reported serious adverse events in both treatment arms were acute kidney injury, pneumonia, heart failure and acute myocardial infarction, with

similar incidence between treatment arms. Similar proportions of patients reported adverse events between T2DM status subgroups.

- 6.33 Important risks associated with dapagliflozin identified in the Periodic Safety Update Report (October 2019 to April 2020) included urinary tract infection, renal impairment, and diabetic ketoacidosis including events with atypical presentation. Important potential risks include liver injury, bladder cancer, breast cancer, prostate cancer, and lower limb amputation.

Benefits/harms

- 6.34 On the basis of the direct evidence presented in the DAPA-CKD trial, for every 100 patients with CKD treated with dapagliflozin plus SOC in comparison with SOC alone, over a median of 28.5 months:
- Approximately 5 fewer patients would experience one event of: $\geq 50\%$ decline in kidney function, progression to ESKD or death related to cardiovascular or renal causes.
 - Approximately 2 fewer patients would experience CKD progression to ESKD.
 - Approximately 4 fewer patients would experience a serious adverse event.

Clinical claim

- 6.35 The submission described dapagliflozin plus SOC as superior in terms of effectiveness compared with SOC alone and non-inferior in terms of safety. The therapeutic conclusion presented in the submission was adequately supported by the clinical evidence, however, the applicability of the results of the DAPA-CKD trial to the Australian setting was uncertain. Differences between the DAPA-CKD trial population and the Australian setting in terms of baseline age, sex, T2DM status, CKD stage (disease progression), and region suggest differences in baseline risk between settings that may impact the absolute magnitude of effect of dapagliflozin in the eligible Australian population. In addition, the larger proportions of males and patients with T2DM in the DAPA-CKD trial may have increased the risk of ESKD compared to the Australian setting.
- 6.36 The PBAC considered that the claim of superior comparative effectiveness was reasonable.
- 6.37 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

- 6.38 The submission presented a cost-utility analysis of dapagliflozin plus SOC versus SOC alone for the treatment of patients with CKD. The economic evaluation was based on *post hoc* analyses of the ITT population of the DAPA-CKD trial, with additional modelled data. The submission also presented a scenario analysis assessing the cost-

effectiveness of dapagliflozin in the subgroup of patients with CKD only (patients with no comorbid diabetes or HFrEF) from the DAPA-CKD trial.

Table 9: Key components of the economic evaluation

Component	Description
Treatments	Dapagliflozin plus SOC; SOC alone
Time horizon	15 years in the model base case versus 29 months in the DAPA-CKD trial
Outcomes	Quality adjusted life years
Methods used to generate results	Markov state transition model
Health states	CKD (stage 2-4) ESKD (conservative care, dialysis, transplant) Death
Cycle length	One month
Transition probabilities	Estimated from extrapolated Kaplan-Meier curves from <i>post hoc</i> analyses of the DAPA-CKD trial for time to ESKD (excluding those who died without experiencing ESKD), time to death (in patients without ESKD), and time from ESKD to death. 96.9% of incremental QALYs and all incremental cost savings occur in the extrapolated period.
Utilities	Based on a <i>post hoc</i> analysis of pooled individual patient-level EQ-5D-5L data from the DAPA-CKD trial. The EQ-5D-5L responses were mapped to EQ-5D-3L and converted to utility index scores using the UK value set. Trial-based estimates were available for CKD stage 2-4, ESKD (conservative care), and ESKD (dialysis). The utility for ESKD (transplant) was based on Lee 2005. The weighted average utility for ESKD was based on proportions of patients receiving ESKD interventions from the published literature (Deloitte 2011; ANZDATA 2020). Utilities from published literature (Jesky 2016; Lee 2005) were used in sensitivity analysis.
Costs	Disease monitoring costs: the frequency of clinician review and laboratory assessments for patients in the CKD and ESKD health states were informed by Australian guidelines (Kidney Health Australia 2020), with unit costs based on various MBS items. ESKD treatment costs: the proportions of patients using each treatment modality were based on the projected proportion of prevalent patients using conservative care (Deloitte 2011) and the relative distribution of dialysis and transplant from ANZDATA 2020. The cost of conservative management was based on Deloitte 2011; the costs of dialysis were based on the distribution of dialysis modalities from ANZDATA 2020 and unit costs from Cass 2010; transplant costs were based on Cass 2010. Adverse events: based on the incidence of serious adverse events of special interest in DAPA-CKD, with unit costs based on selected AR-DRG items. Death: costs of terminal care (hospital- and home-based) were based on estimates from a palliative care provider reported in a 2012 <i>Senate Report on Palliative care in Australia</i> , weighted by the number of palliative care related hospitalisations divided by the number of deaths in 2018.

Source: Table 3.1.1, p99 of the submission.

CKD, chronic kidney disease; EQ-5D-5L, EuroQoL-5 dimension questionnaire, 5 level; ESKD, end-stage kidney disease; QALY, quality adjusted life year; SOC, standard of care

6.39 The model had three health states: chronic kidney disease, ESKD, and death. All patients began the model in the CKD health state, with eGFR between 25 and 75 mL/min/1.73 m². Patients in the CKD health state could remain in their health state, progress to ESKD, or die prior to reaching ESKD. Patients with ESKD could either remain in their health state, or die.

- 6.40 The submission claimed that the model structure was based on a published cost-effectiveness analysis of dapagliflozin in CKD (McEwan et al, 2020), but was simplified, taking into account the most clinically relevant endpoints of CKD (i.e., ESKD and death). The submission argued that models with health states based on every CKD stage are unnecessarily complicated, treatment costs and utilities between CKD stages 2 to 4 are similar (and therefore similar results would be obtained with a single CKD state, compared with a more complex structure), and the simplified model structure allowed for a more robust model that extrapolated directly from Kaplan-Meier data for time to ESKD and survival from the DAPA-CKD trial. The ESC disagreed that a model structure that used separate health states for CKD stages 2, 3 and 4 was unnecessarily complicated. Rather, it considered that it would appropriately capture clinically relevant disease progression of a chronic disease. The ESC also noted that while CKD stages 2-4 may be associated with similar costs and utilities, the submission did not address that the transitions to ESKD would not be similar between different CKD stages. The pre-PBAC response stated that it had validated the model against McEwan et al 2020, and found that it generated cost-effective results with an ICER of \$5,000 to < \$15,000 per QALY gained.
- 6.41 The ESKD health state did not allow transitions between conservative management, dialysis and transplant treatment modalities, which have different costs, survival outcomes and quality of life. The ESC noted that ESKD is not a homogeneous state and agreed with the evaluation that this structural assumption was not appropriate.
- 6.42 Transition probabilities, dapagliflozin treatment discontinuation, and health state utilities were based on the DAPA-CKD trial population. The submission acknowledged differences between the trial population and proposed PBS population in terms of age and sex distribution, and diabetes and heart failure status, but assumed that patient and treatment characteristics from the DAPA-CKD trial would be broadly representative of the target PBS population. Subgroup analyses showed differences in baseline risk for a number of patient characteristics (age, sex, T2DM status, geographical region, and baseline UACR and eGFR categories), and systolic blood pressure was identified as a treatment effect modifier. The ESC considered that differences between the DAPA-CKD trial and the proposed Australian population may result in differences in the underlying risk of patients and their response to dapagliflozin.
- 6.43 Transition probabilities from CKD to ESKD were informed by Kaplan-Meier curves of time to ESKD, excluding patients who died without experiencing ESKD from the DAPA-CKD trial. The model predicted higher proportions of patients with ESKD and death over 29 months than observed in the DAPA-CKD trial for both treatment groups. This appeared to be an artefact of the submission's adjustment to make the estimation of ESKD and death prior to reaching ESKD into mutually exclusive probabilities.
- 6.44 Transition probabilities from CKD to death and from ESKD to death were informed by Kaplan-Meier curves of overall survival in patients with CKD (excluding patients who

reached ESKD) and in patients with ESKD, respectively. The ESC considered that the extrapolated survival estimates did not appear plausible, given that the risks of death modelled in patients with CKD and ESKD were lower than general population estimates. The PSCR argued that the modelled risk of death was only lower than the general population estimates after the 15-year time horizon in the base case model, and thus adjusting for general mortality would have no impact on the ICER in the base case. The ESC acknowledged this, but considered that this further highlighted uncertainty regarding the chosen extrapolation function.

6.45 Key drivers of the economic model are summarised in the table below.

Table 10: Key drivers of the model

Description	Method/Value	Impact
Time horizon (15 Years)	A 15-year time horizon was nominated on the basis that this would represent a lifetime time horizon for patients with CKD. However, based on extrapolated survival curves, the model estimated that 34% of SOC patients and 46% of dapagliflozin with SOC patients remained alive after 15 years. Given the lack of convergence between treatment arms, the model inappropriately converted delayed ESKD and death events into avoided events. The PSCR argued that the modelled evaluation was consistent with the DAPA-CKD results, with a lower proportion of patients with ESKD and death predicted by the model in those treated with dapagliflozin plus SOC compared to SOC alone. Moreover, it argued that it was reasonable to extrapolate the treatment benefit over the 15-year time horizon as the benefit has been previously observed in a randomised controlled trial setting (DECLARE-TIMI 58, Mosenson 2019). The PSCR provided a sensitivity analysis with a 30-year time horizon (mortality adjusted for general population mortality), and various revised inputs, resulting in an ICER of \$█████1 per QALY gained. The ESC disagreed with the PSCR as dapagliflozin may delay time to ESKD and so costs would be delayed rather than avoided. The model was too short, and inappropriately structured, to accurately capture the transitions to ESKD and the cost offsets applied in the 15-year model were not justified.	High, favours dapagliflozin
ESKD transitions	Transition probabilities from CKD to ESKD were informed by Kaplan-Meier curves of time to ESKD, excluding patients who died without experiencing ESKD from the DAPA-CKD trial. Due to the limited observation period in DAPA-CKD, time to ESKD was likely to be primarily informed by patients with more severe disease at baseline. It was therefore unclear whether extrapolations based on the trial period would reflect clinical outcomes over a longer period in a heterogeneous population with varying levels of kidney disease. Alternative modelling of DAPA-CKD data from the published literature (McEwan 2020) suggested a much lower incidence of ESKD when baseline severity was taken into account.	High, favours dapagliflozin

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Description	Method/Value	Impact
ESKD survival	<p>The ESKD health state assumed a fixed distribution of patients receiving different treatment modalities, and transitions between conservative management, dialysis and transplant were not explicitly modelled.</p> <p>The survival estimates in ESKD were informed by sparse data over a limited observation period in the DAPA-CKD trial, in which few patients had received kidney transplant. Extrapolation of these data to inform survival in a mixed cohort over the model time horizon was unlikely to reflect survival in patients over the longer term; or reflect Australian clinical practice, given differences in the use of ESKD treatment modalities. The McEwan 2020 analysis, on which the submission’s model was based, did not rely on DAPA-CKD data to inform survival in the ESKD health state, but used estimates from the published literature to inform mortality and changes in treatment modality.</p> <p>Further, the submission modelled a survival advantage for dapagliflozin in patients with ESKD, which was not consistent with the DAPA-CKD <i>post hoc</i> analysis that informed survival, which showed no statistically significant difference between dapagliflozin and SOC.</p>	High, favours dapagliflozin
Treatment persistence	<p>The submission adjusted the costs of dapagliflozin over time based on a linear extrapolation of treatment persistence estimates from the dapagliflozin arm of the DAPA-CKD trial.</p> <p>The application of treatment persistence as a reduction to drug costs only was inappropriate as treatment persistence would also impact the effectiveness and safety of the treatment (i.e. non-persistent patients would reduce costs but also reduce the benefits/harms of treatment). The PSCR (pp3-4) argued that efficacy results of the DAPA-CKD trial used in the economic analysis were based on an ITT analysis. As such, patients who discontinued treatment in the trial in the dapagliflozin arm were still included in the analysis for all time-to-event outcomes (including ESKD and death). Therefore, the PSCR claimed, the impact of treatment persistence on the effectiveness of dapagliflozin was already accounted for in the time-to-event data used in the economic model. The ESC noted that the model assumed that treatment effects when 87.3% of patients are on treatment at a median follow-up of 18.5 months were the same as when 42.3% of patients are on treatment at 15 years, which was inappropriate, and a major driver of the model.</p>	High, favours dapagliflozin

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Description	Method/Value	Impact
ESKD costs	The ESC noted that the fixed allocation to treatment modalities in the ESKD state may not accurately reflect the relative exposure to each treatment modality, as patients are likely to switch between treatment modalities 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 PSCR (pp3-4) argued that use of ANZDATA prevalence data to inform the proportion of patients in each ESKD state accounted for fluidity between the different treatment modalities for ESKD, and reiterated that costs of dialysis were estimated from an Australia-based costing study (Cass et al, 2010). The ESC noted that a snapshot of data from ANZDATA may not reflect current clinical practice as the available longitudinal data from the ANZDATA registry suggested that treatment patterns for ESKD are changing over time.	High, favours dapagliflozin
	The ESC considered that the cost of dialysis was overestimated as it did not account for the use of haemodialysis in satellite treatment centres (the predominant form of dialysis used in clinical practice).	
	ESKD treatment costs were based on older data, and relied on large inflation factors, which the ESC considered did not reflect current costs in clinical practice.	
	The submission included separate cost items for ESKD monitoring, which appeared to double count the costs associated with clinician review and laboratory monitoring, which were included in source data informing ESKD treatment costs.	

Source: Constructed during the evaluation.

CKD, chronic kidney disease; ESKD, end-stage kidney disease; SOC, standard of care

The redacted values correspond to the following ranges:

¹ \$0 to < \$5,000

6.46 The table below summarises the incremental costs for health care resource items used in the economic evaluation.

Table 11: Disaggregated summary of cost impacts (discounted) in the economic evaluation

Cost description	Dapagliflozin + SOC	Standard of care	Increment
Treatment costs	\$ [REDACTED]	\$1,407	\$ [REDACTED]
- Dapagliflozin	\$ [REDACTED]	\$0	\$ [REDACTED]
- Standard of care	\$ [REDACTED]	\$1,407	\$ [REDACTED]
Monitoring	\$ [REDACTED]	\$13,523	\$ [REDACTED]
- CKD monitoring	\$ [REDACTED]	\$7,623	\$ [REDACTED]
- ESKD monitoring	\$ [REDACTED]	\$5,900	-\$ [REDACTED]
ESKD management	\$ [REDACTED]	\$125,762	-\$ [REDACTED]
- conservative management	\$ [REDACTED]	\$4,790	-\$ [REDACTED]
- dialysis	\$ [REDACTED]	\$88,902	-\$ [REDACTED]
- transplant (initial)	\$ [REDACTED]	\$19,621	-\$ [REDACTED]
- transplant (ongoing)	\$ [REDACTED]	\$12,449	-\$ [REDACTED]
Adverse events	\$ [REDACTED]	\$1,240	-\$ [REDACTED]
Mortality	\$ [REDACTED]	\$2,981	-\$ [REDACTED]
Total	\$ [REDACTED]	\$144,912	-\$ [REDACTED]

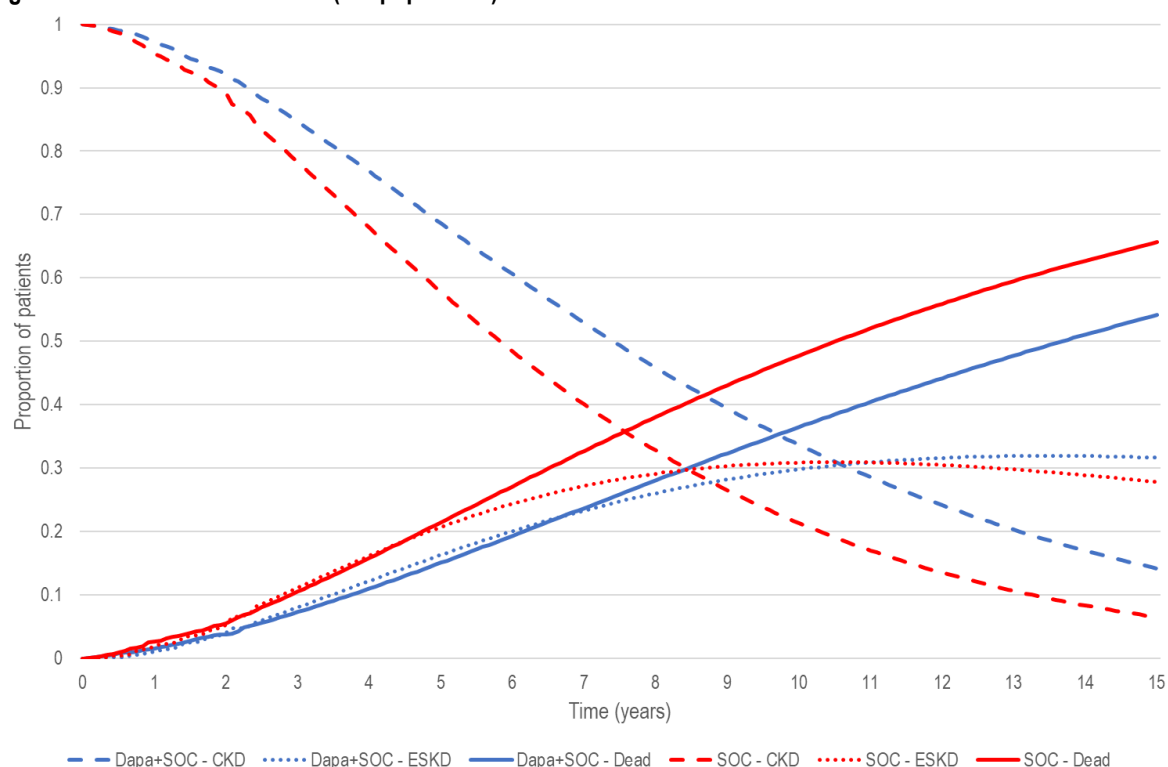
Source: Table 3.8.3, p130 of the submission and 'Dapagliflozin_CKD_CEA_05Mar21_FINAL' TreeAge model provided with the submission
CKD, chronic kidney disease; ESKD, end-stage kidney disease; SOC, standard of care

6.47 The difference in total cost between treatment arms was primarily driven by cost offsets associated with lower ESKD management costs (predominantly dialysis costs) in the dapagliflozin plus SOC arm, which more than offset the additional costs of

dapagliflozin. There was substantial uncertainty in the costs of ESKD due to the assumed fixed distribution of patients among ESKD treatment modalities (17.4% conservative management, 43.0% dialysis, 39.6% transplant), the overestimated costs of dialysis which did not account for haemodialysis in satellite treatment centres, and the use of unit costs based on inflation of older data that may not reflect current costs in clinical practice.

6.48 The model trace for the comparison of dapagliflozin plus SOC with SOC alone in the base case ITT population is presented in Figure 2.

Figure 2: Model trace: base case (ITT population)



Source: Constructed during the evaluation using 'Dapagliflozin_CKD_CEA_05Mar21_FINAL' TreeAge model provided with the submission. CKD, chronic kidney disease; Dapa, dapagliflozin; ESKD, end-stage kidney disease; ITT, intention-to-treat; SOC, standard of care

6.49 The results of the modelled economic evaluation are summarised in Table 12.

Table 12: Results of the economic evaluation: base case (ITT population)

Component	Dapagliflozin + SOC	SOC	Increment
Costs	\$ [REDACTED]	\$144,912	-\$ [REDACTED]
QALYs	6.2431	5.6535	0.5896
Incremental cost/QALY gained			Dapagliflozin dominant

Source: Table 3.8.5, p131 of the submission.

ITT, intention-to-treat; QALY, quality adjusted life year; SOC, standard of care

6.50 Based on the economic model presented in the submission, dapagliflozin with SOC is dominant compared with SOC alone, and is associated with lower costs and improved outcomes.

6.51 Results of the scenario analysis based on the CKD only population are summarised in Table 13 below.

Table 13: Results of the economic evaluation: scenario analysis (CKD only population)

Component	Dapagliflozin + SOC	SOC	Increment
Costs	\$ [REDACTED]	\$184,624	-\$ [REDACTED]
QALYs	6.5020	6.1456	0.3564
Incremental cost/QALY gained			Dapagliflozin dominant

Source: Table 3.9.2, p133 of the submission.

CKD, chronic kidney disease; QALY, quality adjusted life year; SOC, standard of care

6.52 Based on the economic model presented in the submission, dapagliflozin with SOC is dominant compared with SOC alone in the population of patients with CKD only (without comorbid diabetes or heart failure). The ESC advised the results of the analysis were not reliable given: the simplicity of the model structure which did not allow for different transitions to ESKD between different CKD stages; there was limited detail provided to assess the validity of the subgroup analysis; the higher rate of ESKD estimated in this population compared to the DAPA-CKD ITT population, which the ESC considered implausible; and the uncertain cost of ESKD, which used a fixed allocation to treatment modalities and overestimated the cost of dialysis.

6.53 The pre-PBAC response presented additional sensitivity analyses and a revised base-case ICER, shown in the table below.

Table 14: Additional sensitivity analyses and revised base case analysis from the pre-PBAC response

Analysis	Incremental cost	Incremental QALY	ICER
Base case in submission	-\$ [REDACTED]	0.590	Dominant
Plus log-normal function to predict lower rate of ESKD	\$ [REDACTED]	0.558	\$ [REDACTED] ¹
Plus same rate of ESKD-related mortality in both arms	-\$ [REDACTED]	0.481	Dominant
Plus 30-year time horizon and incorporation of lifetables	-\$ [REDACTED]	0.733	Dominant
Plus removal of ESKD monitoring costs	-\$ [REDACTED]	0.733	Dominant
Plus reduction of conservative management and dialysis costs by 10%	\$ [REDACTED]	0.733	\$ [REDACTED] ¹
Revised base case (all of the above + ESKD costs reduced by 50%)	\$ [REDACTED]	0.733	\$ [REDACTED]²
Scenario analysis (all of the above plus with treatment effect of dapagliflozin waning between 29 months and 15 years)	\$ [REDACTED]	0.274	\$ [REDACTED] ³
Revised base case with reduced price (\$ [REDACTED] DPMQ)	-\$ [REDACTED]	0.733	Dominant
Scenario analysis above and reduced price (\$ [REDACTED] DPMQ)	\$ [REDACTED]	0.274	\$ [REDACTED] ²

Source: pre-PBAC response, Table 2, p3.

DPMQ, dispensed price for maximum quantity; ESKD, end-stage kidney disease; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

The redacted values correspond to the following ranges:

¹ \$0 to < \$5,000

² \$5,000 to < \$15,000

³ \$25,000 to < \$35,000

6.54 The dominance of dapagliflozin resulted from the incremental cost of dapagliflozin treatment being lower than the incremental costs of ESKD treatment. The sensitivity analyses therefore focussed on variables that affected the costs of dapagliflozin treatment and the costs of ESKD, as summarised in the table below.

Table 15: Results of sensitivity analyses (note – these are not updated with the pre-PBAC response price offer)

Analysis	Incremental cost	Incremental QALYs	ICER
Base case	-\$ [redacted]	0.5896	Dapagliflozin dominant
Time horizon (base case 15 years)			
20 years	\$ [redacted]	0.7588	\$ [redacted] ⁴
40 years	\$ [redacted]	1.0087	\$ [redacted] ⁵
Transition probabilities: CKD to ESKD (base case: extrapolation using gamma parametric function)			
Extrapolation based on Gompertz parametric function	\$ [redacted]	0.4834	\$ [redacted] ⁶
Extrapolation based on Weibull parametric function	-\$ [redacted]	0.6045	Dapagliflozin dominant
Extrapolation based on exponential parametric function	-\$ [redacted]	0.5845	Dapagliflozin dominant
Extrapolation based on log-logistic parametric function ¹	\$ [redacted] ²	0.5774	\$ [redacted] ⁷
Extrapolation based on log-normal parametric function	\$ [redacted]	0.5584	\$ [redacted] ⁷
Transition probabilities: ESKD to death (base case: extrapolation using Weibull parametric function)			
Extrapolation based on Gompertz parametric function	-\$ [redacted]	0.4855	Dapagliflozin dominant
Extrapolation based on exponential parametric function	\$ [redacted]	0.6728	\$ [redacted] ⁴
Extrapolation based on log-logistic parametric function	-\$ [redacted]	0.5420	Dapagliflozin dominant
Extrapolation based on log-normal parametric function ¹	-\$ [redacted]	0.4761	Dapagliflozin dominant
Extrapolation based on gamma parametric function	\$ [redacted]	0.6180	\$ [redacted] ⁷
ESKD management distribution (base case: 17.4% conservative management (Deloitte 2011 prevalence); 43.0% dialysis and 39.6% transplant (ANZDATA 2020 prevalence))			
Conservative management 17.4% from Deloitte 2010; distribution between dialysis (54.4%) and transplant (28.2%) based on ANZDATA incidence data ¹	-\$ [redacted]	0.5902	Dapagliflozin dominant
Conservative management 50% (AIHW 2016; incidence); distribution between dialysis (32.9%) and transplant (17.1%) based on ANZDATA incidence data	\$ [redacted]	0.5880	\$ [redacted] ⁷
DAPA-CKD trial (Table 2.5.1; 34.1% conservative management; 61.9% dialysis; 4.1% transplant) ¹	-\$ [redacted]	0.5900	Dapagliflozin dominant
Double conservative management (34.8%); distribution between dialysis (33.9%) and transplant (31.3%) based on ANZDATA prevalence data.	\$ [redacted]	0.5885	\$ [redacted] ⁷
Dapagliflozin discontinuation (base case: monthly discontinuation of 0.48% applied for 10 years applied to drug costs only)			
Dapagliflozin discontinuation applied for median duration of trial – 29 months (as no adjustment to treatment effects for further discontinuation beyond trial duration)	-\$ [redacted]	0.5896	Dapagliflozin dominant
ESKD costs (base case: transplant \$99,058; ESKD monitoring \$230.23; ESKD treatment \$4,142 per cycle)			
Cost of ESKD monitoring \$0 (captured in costs of ESKD treatment)	-\$ [redacted]	0.5896	Dapagliflozin dominant
ESKD treatment and transplant costs \$0 ³	\$ [redacted]	0.5896	\$ [redacted] ⁵
Cost dialysis \$7,292.66/cycle (including cost/proportions of patients receiving dialysis at satellite centres); Weighted average cost of ESKD treatment \$3,808.59	-\$ [redacted]	0.5896	Dapagliflozin dominant

Source: Table 3.9.2, p133 of the submission and 'Dapagliflozin_CKD_CEA_05Mar21_FINAL' TreeAge model provided with the submission AIHW, Australian Institute of Health and Welfare; CKD, chronic kidney disease; ESKD, end-stage kidney disease; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

¹ Sensitivity analysis presented by the submission; the remaining analyses were conducted during evaluation.

² Corrected during the evaluation; the submission incorrectly claimed this analysis was cost saving, and resulted in dapagliflozin being dominant.

³ Presented to show impact, noting this is not a clinically plausible scenario.

The redacted values correspond to the following ranges:

⁴ \$5,000 to < \$15,000

⁵ \$15,000 to < \$25,000

⁶ \$35,000 to < \$45,000

⁷ \$0 to < \$5,000

6.55 The sensitivity analyses indicated that the model was most sensitive to time horizon, the parametric functions used to estimate progression to ESKD and from ESKD to death, the distribution between treatment modalities in ESKD, the costs of ESKD treatment, and treatment persistence. However, the ESC advised that without a revised model structure and extrapolation, which parameters may be more important could not be adequately assessed in sensitivity analyses. Even though the DAPA-CKD trial was positive and sensitivity analyses suggested dapagliflozin would remain cost-effective, the ESC felt that the considerable uncertainty in the way the model was structured meant these analyses were unreliable.

Drug cost/patient/year

6.56 The dapagliflozin drug cost per year was \$ [REDACTED] per patient per year based on the revised price offer in the pre-PBAC response and 13.045 scripts per patient per year, assuming 100% compliance. The estimated drug costs differed between the economic analysis and financial estimates due to differences in assumptions relating to treatment adherence and persistence. The original and revised DPMQs are shown in the table below.

Table 16: Drug cost per patient per year for dapagliflozin

	DAPA-CKD trial	Economic model	Financial estimates
Daily dose	10 mg daily	10 mg daily	10 mg daily
Cost per pack of 28 tablets (submission DPMQ)	-	\$ [REDACTED]	\$ [REDACTED]
Cost per pack of 28 tablets (pre-PBAC response price) ¹	-	\$ [REDACTED]	\$ [REDACTED]
Adherence	98.6%	100%	98.6%
No. scripts per year	-	13.045 (=365.25 ÷ 28 x 100%)	12.862 (=365.25 ÷ 28 x 98.6%)
Cost per year (submission DPMQ)	-	\$ [REDACTED]	\$ [REDACTED]
Cost per year (pre-PBAC response price) ¹	-	\$ [REDACTED]	\$ [REDACTED]
Proportion of patients on treatment (persistence)	At a median follow-up of 18.5 months, 87.3% of patients in the dapagliflozin arm remained on treatment	Year 1: 94.4% Year 2: 89.2% Year 3: 84.2% Year 4: 79.5% Year 5: 75.1% Year 6: 70.9%	100%

Source: Table 14.1.1, p10 CSR appendices, Dapa CKD model inputs_05Mar2021 and Attachment4.1_DAPA_CKD_BIM spreadsheets provided with submission

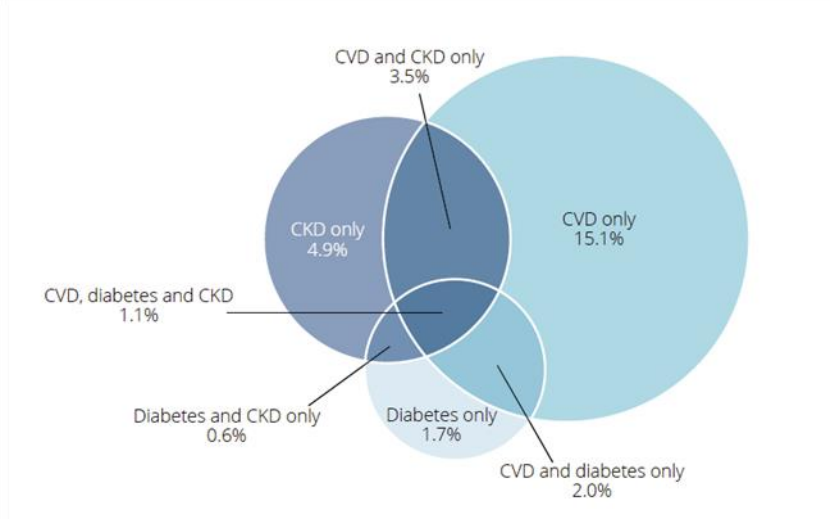
DPMQ, dispensed price for maximum quantity

¹ The pre-PBAC response offered a DPMQ of \$ [REDACTED], consistent with the [REDACTED] price. The [REDACTED] DPMQ at the time of the July 2021 PBAC meeting was \$ [REDACTED].

Estimated PBS usage & financial implications

- 6.57 This submission was considered by DUSC. The submission used an epidemiological approach to estimate the utilisation and financial impacts associated with the PBS listing of dapagliflozin for the treatment of CKD, in the CKD only population. Patients likely to be treated with dapagliflozin for T2DM under existing PBS listings or the proposed PBS listing for HFrEF (item 7.01 refers) were excluded.
- 6.58 The submission estimated the Australian CKD population based on a review of eGFR and UACR biomedical data from 2011-2012 National Health Measures Survey (NHMS) assuming the eligible CKD population to be equivalent to the sum of the proportions of patients with CKD biomedical data consistent with CKD stages 2 to 3b, as a proxy for the clinical criteria; eGFR ≥ 25 and ≤ 75 mL/min/1.73 m². The proportion of patients likely to be diagnosed were based on the proportions of self-reported CKD disease in the 2011-2012 Australian Health Survey.
- 6.59 The submission acknowledged that the listing of dapagliflozin for the treatment of CKD may increase the incidence of diagnosed CKD, and assumed an annual increase of 2% in the rate of diagnoses over 6 years of listing. In addition, the submission assumed that ■% of patients currently treated with empagliflozin who will be eligible for PBS subsidised dapagliflozin for CKD, will switch to dapagliflozin. The savings derived from patients switching from empagliflozin were offset against the costs of dapagliflozin.
- 6.60 The proportions of patients likely to be eligible for treatment with dapagliflozin under the existing T2DM or the proposed HFrEF PBS listings were calculated individually, using the proportions of overlapping populations suggested in the *AIHW Cardiovascular disease, diabetes and chronic kidney disease: Australian facts report* (2014; figure shown below), and the estimated prevalence of uncontrolled T2DM and cardiovascular disease attributable to HFrEF in the Australian CKD population.

Figure 3: Overlap between heart failure, chronic kidney disease and type 2 diabetes mellitus



Source: Figure 5.1.1 of the submission, p161, from Kidney Health Australia 2020; adapted from AIHW 2014. CKD, chronic kidney disease; CVD, cardiovascular disease; T2DM, Type 2 diabetes mellitus. Estimated overlap is relevant to patients aged 18 and older.

- 6.61 The PBAC noted that using the figure above, the proportion of the Australian population with CKD (with or without comorbidities) is 10.1%, and assuming that the heart failure (HF) population is 10% of the CVD population (Liew et al 2020), then it is possible to deduce that the proportion with CKD and T2DM only is 1.59% and the proportion with CKD, T2DM and HF is 0.11%. Thus, the proportion of people with CKD that also have T2DM could be $(1.59\% + 0.11\%) / 10.1\% = 16.8\%$. This means that the proportion of CKD patients not eligible under the T2DM restriction could be as low as 83.2%, although the PBAC acknowledged that this estimate did not explicitly account for eligibility according to the existing and proposed PBS restrictions.
- 6.62 The submission estimated savings to Commonwealth, State and Territory government health budgets from ESKD events avoided (transplant, dialysis, conservative management) in patients treated with dapagliflozin, based on the annualised rate of ESKD events reported in the dapagliflozin plus SOC and SOC treatment arms of the DAPA-CKD trial. The annualised costs of ESKD events calculated for the economic evaluation were applied in the financial estimates. The costs to the Commonwealth and State or Territory government budgets were not estimated separately.
- 6.63 Key inputs used to derive the financial estimates are presented in the table below.

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Table 17: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Australian adults (%) with biomedical data suggesting CKD	Assumed prevalence of 10%, based on patient biomedical data (2011-12 NHMS) and KHA (2012) definition of CKD Year 1: 2,075,792 to Year 6: 2,239,310	This may be reasonable, but was uncertain, as biomedical data may not have identified the difference between chronic and acute kidney disease
Adults (%) with biomedical data suggesting CKD, likely to be diagnosed with CKD	Rate of diagnosis of 10% based on survey of self-reported kidney disease Year 1: 10% (2011-12 AHS) Assumed annual 2% increase to Year 6: 20%	Self-reported diagnosis of CKD may not be reliable. Revised in the pre-PBAC response to annual 5% increase to Year 6: 35%
Adults (%) with CKD stages 1-5	CKD 1: 3.9%; CKD 2: 2.5%; CKD 3a: 2.7%; CKD 3b: 0.6%; CKD 4-5: 0.3% (2011-12 NHMS 2013)	The estimates were based on older 2011-2012 biomedical data (NHMS 2013) and were highly uncertain
Adults diagnosed with CKD in CKD stages 2-3b	Assumed based on biomedical data (2011-12 NHMS) 5.8% (sum of % undiagnosed CKD 2-3b) 58% (% of diagnosed CKD; 0.058 / 0.10)	The submission assumed that proportions of patients with biomedical markers for CKD stages from undiagnosed population can be applied to the prevalence of diagnosed (self-reported) CKD; and that CKD 2-3b is a reasonable proxy for clinical criteria (eGFR ≥ 25 to ≤ 75 mL/min/1.73 m ² ; and UACR ≥ 200 and ≤ 5000 mg/g), when it includes some patients with less severe disease (CKD 2), and excludes some patients with severe disease (CKD 4). May have overestimated numbers of eligible patients given the large numbers of patients with eGFR 75-89 mL/min/1.73 m ² , and limited overlap with the PBS population in terms of albuminuria.
Adults (%) with biomedical data suggesting CKD, with/without overlapping comorbidities of T2DM and/or CVD	CKD only: 4.9% CKD + CVD: 3.5% CKD + T2DM: 0.6% CKD + CVD + T2DM: 1.1% (2011-12 AHS)	2011-2012 AHS data is the most recent reliable Australian data, but may not reflect current Australian setting. Estimates were based on older 2011-2012 biomedical data (NHMS 2013) and were highly uncertain.
Proportion of CKD patients not eligible for PBS-listed SGLT2 inhibitors for T2DM (HbA1c $\leq 7.0\%$)	93.4% based on following factors: Diabetics with T2DM: 88% (AUSDIAB 2012) T2DM eligible for SGLT2i: 44.4% (AUSDIAB 2012) Morbidity overlap CKD + T2DM: 0.6%; and CKD + CVD + T2DM: 1.1% (2011-12 AHS)	The calculations used were complex, and used multiple factors from different sources and populations. It was assumed that estimates of age-standardised prevalence related to T2DM and HFREF in the Australian population using older data (2011-2012) could be applied to the eligible CKD prevalent population. Estimates were highly uncertain and substantially underestimated the proportions of CKD patients likely to be treated with dapagliflozin for T2DM or HFREF. (97.4% was revised to 97.7% in the pre-PBAC response).
Proportion of CKD patients not eligible for PBS-listed dapagliflozin for HFREF	97.4% based on the following factors: Adults with CVD: 22% (AIHW 2014) Adults with HF: 2.2% (Liew et al. 2020) HF likely to be HFREF: 57% (SNAPSHOT-HF data) Morbidity overlap CKD + CVD: 3.5%; and CKD + CVD + T2DM: 1.1% (2011-12 AHS)	The calculations used were complex, and used multiple factors from different sources and populations. It was assumed that estimates of age-standardised prevalence related to T2DM and HFREF in the Australian population using older data (2011-2012) could be applied to the eligible CKD prevalent population. Estimates were highly uncertain and substantially underestimated the proportions of CKD patients likely to be treated with dapagliflozin for T2DM or HFREF. (97.4% was revised to 97.7% in the pre-PBAC response).
Treatment adherence	98.6% for dapagliflozin and empagliflozin	Derived from the DAPA-CKD trial. May not be applicable to clinical practice

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Parameter	Value applied and source	Comment
Treatment utilisation		
Uptake of dapagliflozin	█% in Year 1 increasing to █% in Years 3-6	Assumed. Revised in the pre-PBAC response: Year 1-6=█%, █%, █%, █%, █%, █%.
Proportion of patients with CKD taking SGLT2 inhibitors (SGLT2i) for T2DM	Assumed to be equivalent to the population excluded as eligible for SGLT2i therapies █% (█-█%) Assumed empagliflozin █%; dapagliflozin █%	Assumed. The use of SGLT2i was assumed to be equivalent to the population excluded as eligible for SGLT2i therapies for T2DM, and was highly uncertain.
Empagliflozin users switching to dapagliflozin	█%	Assumed
ESKD events avoided per year per 100 patients	ESKD: 1.07% Transplant: 39.6% Dialysis: 43% Conservative management: 17.4%	Derived from Section 3.6 of the economic evaluation.
Annual cost of transplant	Year 1: \$113,780; subsequent years: \$14,722	
Annual cost of dialysis	\$96,821	
Annual cost conservative management	\$12,891	

Source: Tables 4.1.1 and 4.2.1, p.134 and 138 of the submission

ACEI, angiotensin converting enzyme inhibitor; AHS, Australian Health Survey; AIHW, Australian Institute of Health and Welfare; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; CVD, cardiovascular disease; DAPA, dapagliflozin; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HbA1c, haemoglobin A1c; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; KHA, Kidney Health Australia; SGLT2i, sodium glucose co-transporter-2 inhibitor; SOC, standard of care; T2DM, Type 2 diabetes mellitus

6.64 Table 18 summarises the estimated eligible population, and the net cost to the R/PBS, of listing dapagliflozin for the treatment of CKD, based on the submission’s DPMQ of \$█.

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Table 18: Estimated eligible population and net cost to the R/PBS of listing dapagliflozin for CKD

Description	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Australian adult population	20,757,917	21,082,471	21,411,852	21,744,502	22,073,220	22,393,101
Total CKD population (10%)	2,075,792	2,108,247	2,141,185	2,174,450	2,207,322	2,239,310
Diagnosed CKD (10-20%)	207,579	252,990	299,766	347,912	397,318	447,862
CKD stages 2-3b (58%)	120,396	146,734	173,864	201,789	230,444	259,760
Patients not eligible for PBS SGLT2 inhibitors (93.4%)	112,399	136,988	162,316	188,386	215,138	242,506
Patients not eligible for PBS-listed dapagliflozin for HFrEF (97.4%)	109,453	133,397	158,062	183,448	209,499	236,150
Uptake (assumed)	%	%	%	%	%	%
Estimated treated patients	¹	²	³	³	³	³
Patients switching from PBS-listed empagliflozin	⁴	⁴	⁴	⁵	⁵	⁵
Estimated total patients	¹	²	³	³	³	³
Total scripts (12.86/patient/year)	⁶	⁷	⁷	⁷	⁷	⁸
Cost to R/PBS (less co-payment)	\$ ⁹	\$ ¹⁰	\$ ¹¹	\$ ¹¹	\$ ¹¹	\$ ¹²
Net savings of empagliflozin (less co-payment)	-\$ ¹³	-\$ ¹³	-\$ ¹³	-\$ ¹³	-\$ ¹³	-\$ ¹³
Net cost to R/PBS (less co-payment)	\$ ⁹	\$ ¹⁰	\$ ¹¹	\$ ¹¹	\$ ¹¹	\$ ¹¹
Total cost of ESKD avoided	-\$ ¹¹	-\$ ¹²	-\$ ¹⁴	-\$ ¹⁵	-\$ ¹⁶	-\$ ¹⁶
Net savings to Commonwealth, State and Territory governments	-\$ ¹¹	-\$ ¹¹	-\$ ¹²	-\$ ¹²	-\$ ¹⁴	-\$ ¹⁴

Source: Tables 4.2.2, 4.2.3, 4.2.4, 4.2.6, 4.2.10, and 4.4.1, pp.139-154 of the submission

CKD, chronic kidney disease; ESKD, end-stage kidney disease, HFrEF, heart failure with reduced ejection fraction; SGLT2, sodium glucose co-transporter-2

The redacted values correspond to the following ranges:

- ¹ 50,000 to < 60,000
- ² 80,000 to < 90,000
- ³ 100,000 to < 200,000
- ⁴ 500 to < 5,000
- ⁵ 5,000 to < 10,000
- ⁶ 700,000 to < 800,000
- ⁷ 1,000,000 to < 2,000,000
- ⁸ 2,000,000 to < 3,000,000
- ⁹ \$60 million to < \$70 million
- ¹⁰ \$90 million to < \$100 million
- ¹¹ \$100 million to < \$200 million
- ¹² \$200 million to < \$300 million
- ¹³ \$0 to < \$10 million

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¹⁴ \$300 million to < \$400 million

¹⁵ \$400 million to < \$500 million

¹⁶ \$500 million to < \$600 million

- 6.65 The submission estimated a total of 50,000 to < 60,000 patients in Year 1, increasing to 100,000 to < 200,000 patients in Year 6 of listing, including patients with T2DM switching from empagliflozin to dapagliflozin (500 to < 5,000 in Year 1 to 5,000 to < 10,000 in Year 6).
- 6.66 The estimated net cost to the R/PBS of listing dapagliflozin for CKD (including offsets for empagliflozin) was \$60 million to < \$70 million in Year 1, increasing to \$100 million to < \$200 million in Year 6, an estimated net cost of \$800 million to < \$900 million over the first six years of listing.
- 6.67 The submission estimated a total savings to government health budgets associated with a reduction in ESKD events of \$100 million to < \$200 million in Year 1, increasing to \$500 million to < \$600 million in Year 6 of listing, and an overall net savings to Commonwealth, State and Territory governments of > \$1 billion over six years. Costs to the Commonwealth and State/Territory government budgets were not estimated separately. The majority of costs associated with ESKD would be incurred by State/Territory governments.
- 6.68 The evaluation and the DUSC considered the estimated utilisation and net cost of listing dapagliflozin for CKD on the PBS were highly uncertain for the following reasons:
- The estimated eligible CKD population in the Australian setting and progression of CKD in the eligible population may not be reliable, given the limitations of the 2011-2012 NHMS (2013) and 2011-2012 AHS (2013) data, in terms of age of the data, the potential inclusion of AKI and other transient kidney disease, and the reliance on self-reported diagnoses of CKD. In addition, the use of CKD stage 2-3b data as a proxy for the clinical eligibility criteria may overestimate the overall eligible CKD population. The PBAC noted the NHMS acknowledged that it did not review duration of CKD markers, and may have counted data unrelated to CKD (e.g. AKI, kidney/urogenital infection). As noted in Table 17, the use of CKD stage 2-3b disease as a proxy for the clinical criteria (i.e. eGFR ≥ 25 and ≤ 75 mL/min/1.73 m²; and UACR ≥ 200 and ≤ 5000 mg/g) included additional patients with CKD stage 2 disease, and excluded patients with CKD stage 4 disease in the estimated eligible population. The submission acknowledged that this approach may have overestimated the financial impact because the proportion of patients with stage 2 disease is a noticeably larger cohort than the proportion with stage 4 disease. However, it suggested that because the data was based on eGFR/UACR measured data not actual diagnoses, and CKD is an underdiagnosed condition particularly in earlier stages of the disease, the submission's approach "would balance any difference in CKD stage proportions between measured and

diagnosed populations”. The PBAC noted that in the NHMS, 6.7% were estimated to have microalbuminuria (males 2.5–25 mg/mmol and females 3.5–35 mg/mmol), and only 0.9% (males >25 mg/mmol and females >35 mg/mmol) were estimated to have macroalbuminuria. It considered that very few patients with microalbuminuria were likely to meet the PBS eligibility criteria of 22.6–565 mg/mmol, and therefore the 5.8% used by the submission to determine eligibility was likely vastly overestimated.

- The sources and methods used to estimate the overlapping proportions of eligible CKD patients who would also be eligible for dapagliflozin under the existing T2DM or the proposed HFrEF listings, may not be reliable:
 - The calculations used to determine the proportions of patients likely to be treated with PBS subsidised dapagliflozin for T2DM and HFrEF were complex, used multiple factors from different sources and populations, and assumed that age-standardised estimates of prevalence related to T2DM and HFrEF in the Australian population using older data (2011-2012) could be applied to the eligible CKD prevalent population. The estimates were highly uncertain and may underestimate the proportions of CKD patients likely to be treated with dapagliflozin for T2DM or HFrEF;
 - The eligible CKD population with overlapping eligibility for both T2DM and HFrEF (CKD + T2DM + HFrEF) was included in the calculations for both T2DM and HFrEF.
- The estimated savings to government health budgets from ESKD avoided assumed the benefits of dapagliflozin observed in the DAPA-CKD trial over 28.5 months, in terms of delayed time to ESKD, would remain constant over the first 6 years of listing. Delayed time to ESKD for patients treated with dapagliflozin was interpreted as avoidance of this outcome in the financial estimates. DUSC considered that the costs associated with ESKD would be delayed, but not avoided.

6.69 DUSC considered the estimates presented in the submission to be underestimated. Among other matters, it considered the main issues were:

- an underestimation of the diagnosis rate of CKD, noting the increasing screening and diagnosis for CKD in general practice;
- an underestimation of the uptake rate by eligible patients; and
- an underestimation of the duration of treatment, which it expected to be longer due to emphasis on early detection and management and the absence of a stopping rule in the restriction.

6.70 However, the PBAC noted the DUSC did not recognise that using CKD stage 2-3b as a proxy for PBS population had vastly overestimated eligible patients based on microalbuminuria criteria (see paragraph 6.68). The PBAC also noted that other

conditions excluded from the trial were not deducted from the estimated eligible PBS population.

- 6.71 The pre-PBAC response provided revised financial estimates which:
- included the revised DPMQ of \$█████;
 - increased the increment of diagnosed CKD from 10% in Year 1 plus 2% increase each year (10-20%), to a 5% increase each year (10-35%);
 - increased uptake from █████-████% over six years to █████-████% over six years; and
 - increased the percentage of patients not eligible for PBS-listed dapagliflozin for HFREF from 97.4% to 97.7%, by narrowing the CKD overlap with HFREF patients (LVEF<40%) to those *in NHYA Classes II-IV receiving SOC*.
- 6.72 These changes increased the eligible population from 100,000 to < 200,000 in Year 6 to 400,000 to < 500,000 in Year 6. Given the methods used to estimate patients switching from empagliflozin, these patients also increased from 5,000 to < 10,000 in Year 6 to 10,000 to < 20,000 in Year 6. In the pre-PBAC response, the net cost to the R/PBS (including offsets for empagliflozin) was \$40 million to < \$50 million in Year 1, increasing to \$200 million to < \$300 million in Year 6, an estimated net cost of \$700 million to < \$800 million over the first six years of listing.
- 6.73 The pre-PBAC response presented two scenarios for savings to government health budgets associated with a reduction in ESKD costs – a 10% reduction and a 50% reduction from the submission base case. The “10% reduction” resulted in savings of \$200 million to < \$300 million in Year 1, increasing to > \$1 billion in Year 6 of listing, and an overall net savings to Commonwealth, State and Territory governments of > \$1 billion over six years. The “50% reduction” resulted in savings of \$100 million to < \$200 million in Year 1, increasing to \$800 million to < \$900 million in Year 6 of listing, and overall net saving of > \$1 billion over six years.
- 6.74 The pre-PBAC response also provided an analysis incorporating the proportion of patients who would stop treatment at the initiation of renal replacement therapy (in line with a potential stopping rule in the restriction). The pre-PBAC response stated that the proportions discontinuing due to transplant or dialysis per year were derived from the model, but the PBAC noted that these values had not been evaluated, and it was unclear how they were obtained.

Quality Use of Medicines

- 6.75 The sponsor stated that comprehensive education will be provided for health care workers and patients, and that activities to support the quality use of medicines and post-marketing surveillance for dapagliflozin are in development. DUSC considered that for SGLT2 inhibitors there remains further need for GP education and support for peri-procedural practice and ketoacidosis, candidiasis and urinary symptoms.

Financial Management – Risk Sharing Arrangements

- 6.76 The PSCR proposed a Risk Sharing Arrangement (RSA). The PSCR claimed that the restriction wording, a proposed weighted price, and an RSA would address the risk of leakage. The pre-PBAC response was of the strong opinion that a price reduction to [REDACTED] the [REDACTED] DPMQ negated the need for an RSA, as it would alleviate the risk of leakage between T2DM, HFrEF and CKD. The PBAC considered that the revised price did not address the risk of uncertain financial impact in a situation where the R/PBS impact would remain high even after the estimated eligible population was greatly reduced (see paragraph 6.70).

Additional Information

- 6.77 The sponsor presented the estimated combined financial implications to the PBS and health budgets of listing dapagliflozin for the treatment of HFrEF and CKD in Section 5 of both submissions. The approach attempted to account for the existing Type 2 diabetes population, and the overlap between the proposed HFrEF and CKD populations. The PBAC considered revisions to these estimates were required to account for the eligible CKD population, the projected utilisation for T2DM, and the revised price offer.

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

7 PBAC Outcome

- 7.1 The PBAC deferred making a recommendation for dapagliflozin for the treatment of patients with chronic kidney disease. The PBAC is satisfied that dapagliflozin added to standard care provides, for some patients, a significant improvement in efficacy over standard care alone. The PBAC considered that the listing would be cost effective at the price proposed in the pre-PBAC response (the [REDACTED] price for dapagliflozin for [REDACTED]), and it was therefore of a mind to recommend a General Schedule Authority Required (Streamlined) listing. However, the PBAC remained concerned about the uncertainty of the estimated financial impact (considering that the R/PBS cost would be high even once the eligible population was greatly reduced as per PBAC advice). The PBAC noted that the proposed population was broader than the DAPA-CKD trial population, and considered that the PBS listing would need to be restricted to those in whom clinical effectiveness had been established and for whom there was no alternative therapy available. The PBAC also noted that although the submission had

presented additional information to estimate the overall net impact of listing for both CKD and HFrEF (see agenda item 7.01, July 2021 PBAC meeting), it had not provided estimates for total dapagliflozin PBS utilisation including T2DM. The PBAC considered that these estimates were necessary to inform its advice to the Australian Government about an appropriate RSA to ensure that the subsidy of dapagliflozin is restricted to the populations in whom PBAC has considered it cost effective. The PBAC therefore requested that the department obtain these estimates from the sponsor before it reconsidered this submission for CKD (and the resubmission for HFrEF).

- 7.2 The PBAC recognised that there was a high and urgent unmet clinical need for effective treatments for CKD, noting that there were limited effective therapies on the PBS specifically for treatment of this life-threatening condition.
- 7.3 The PBAC noted that the proposed restriction was aligned with the DAPA-CKD trial in terms of eGFR and UACR eligibility. The PBAC agreed with the ESC that UACR should be expressed both in mg/g and mg/mmol as both are reported in pathology laboratories in Australia (200 – 5,000 mg/g; 22.6 – 565 mg/mmol). Furthermore, the PBAC agreed with the ESC that the restriction should specifically require that the patient must have sustained evidence of CKD for three months. In line with the trial exclusion criteria and the TGA delegate’s recommended warning, the PBS restriction should also exclude: 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. The PBAC considered that there was uncertain clinical effectiveness and cost effectiveness in these groups given their exclusion from the trial and there may be different comparators available via the PBS for some of these patients. The PBAC noted that patients with T1DM were excluded from the trial, and that the current dapagliflozin PI warns against use in this group. Given the relatively long clinical experience with dapagliflozin, the PBAC did not consider it necessary to exclude this group from the CKD listing, noting that this would be consistent with the T2DM listing, which also does not explicitly exclude these patients. The PBAC noted that the proposed maximum quantity of one pack with five repeats would provide for six months’ treatment, which was suitable for a chronic condition and consistent with the dapagliflozin listings for T2DM. The PBAC noted that the listing in section 3 will need to be updated to include its advice.
- 7.4 The PBAC noted the submission’s proposed restriction did not include stopping criteria, and noted the advice provided in the pre-PBAC response and the sponsor hearing with respect to this issue. The PBAC considered that it would be appropriate to cease treatment on commencement of renal replacement therapy given the lack of evidence to support continued use in this population, but that the restriction need not require patients to cease therapy when their eGFR declined below 25 mL/min/1.71 m².
- 7.5 The PBAC agreed with the submission’s nominated comparator of standard of care,

noting that ACEIs and ARBs (unless contraindicated) are the only pharmacological interventions commonly recommended for the treatment CKD in clinical guidelines.

- 7.6 The PBAC agreed with the submission's positioning of dapagliflozin as an addition to standard of care in CKD, administered concurrently with an ACEI or ARB (unless contraindicated). Although there were relatively few patients not receiving an ACEI/ARB in DAPA-CKD, the PBAC agreed with the sponsor hearing that patients with contraindications to these therapies would still be expected to benefit from dapagliflozin and that they had even greater need for an effective treatment option as existing standard of care was unsuitable for them. The PBAC noted that the listing in section 3 will need to be updated to include its advice.
- 7.7 In terms of the clinical evidence presented, the PBAC agreed with the ESC that there were issues with the DAPA-CKD trial in terms of its likely applicability to the Australian population, and that the *post hoc* CKD only subgroup analysis was unreliable. Nonetheless, the PBAC agreed with the evaluation's conclusion that dapagliflozin plus SOC was superior in terms of effectiveness compared with SOC alone and non-inferior in terms of safety. It considered that dapagliflozin provided a substantial added benefit in terms of a reduction in ESKD and death (see Tables 4 and 5 above). Although there were uncertainties with respect to the clinical evidence, these affected the interpretation of the magnitude of benefit in parts of the Australian CKD population and not the existence of an overall benefit in the eligible trial population, which was adequately supported by the trial data with a high level of certainty. The PBAC considered that the issues identified by ESC were less critical to its decision making given the price reduction to [REDACTED] the [REDACTED] price in [REDACTED], as discussed further below.
- 7.8 The submission presented a cost-utility analysis of dapagliflozin plus SOC versus SOC alone. The PBAC noted that the simple model structure combined different CKD stages into a single CKD health state and did not allow for transitions through CKD stages or between treatment modalities in ESKD. It agreed with the ESC that the model structure was poorly justified, and overly simple. It also considered that the model had a number of other issues with respect to its time horizon, application of treatment persistence, and ESKD transitions, survival and costs (see Table 10 and paragraph 6.52 for details). The PBAC acknowledged the various sensitivity analyses put forward in the pre-PBAC response, and noted minimal variation from the base case analysis, but considered that this did not overcome the fundamental issues with the model structure and reduced confidence in the resulting ICERs. The PBAC noted that in the revised base case presented in the pre-PBAC response, incorporating the price reduction to [REDACTED] the [REDACTED] price and various other adjustments, dapagliflozin remained dominant (see Table 14). The PBAC remained concerned that the model structure was not robust, however, at the reduced price the Committee was confident that the ICER would be in an acceptable range, comparable to other

treatments for chronic conditions. Overall, the PBAC considered a CKD listing would be cost effective at the [REDACTED] price.

- 7.9 In terms of the financial implications, the PBAC agreed with the evaluation that several uncertainties existed including the estimation of the eligible population, the estimation of the overlapping populations with T2DM and HFREF, and the estimated net savings to government health budgets from ESKD delayed (paragraph 6.68). It also agreed with the DUSC that the diagnosis rate, uptake rate and duration of treatment were likely underestimated, and considered that the adjustments made with respect to these inputs in the pre-PBAC response were appropriate. The PBAC considered that treatment duration would in part be determined by a requirement in the restriction to cease treatment on commencement of renal replacement therapy, and noted that although the pre-PBAC response had provided an appropriate scenario analysis, it was unclear how the proportion of discontinuing patients were derived, and this would need to be clarified in revised estimates obtained from the sponsor.
- 7.10 Although the price reduction and other adjustments in the pre-PBAC response reduced the overall estimated R/PBS impact to \$700 million to < \$800 million over six years, the PBAC considered that the eligible population had been vastly overestimated. Specifically, the PBAC considered that the use of CKD stage 2-3b disease in the NHMS as a proxy for the PBS clinical criteria (i.e. eGFR ≥ 25 and ≤ 75 mL/min/1.73 m²; and UACR ≥ 200 and ≤ 5000 mg/g) had included a likely substantial number of patients who would not be eligible for PBS subsidy in terms of albuminuria. The eligible population would be closer to 0.9% than 5.8% of undiagnosed CKD, that is closer to 9% than 58% of diagnosed (see paragraph 6.68). In addition, the NHMS may have included patients with transient disease, and would have also counted other patients the PBAC recommended be excluded from the restriction (those noted in paragraph 7.3), who would need to be excluded from revised estimates.
- 7.11 In terms of the overlapping population with T2DM, the PBAC noted that based on assumptions around Figure 5.1.1 of the submission (a figure adapted from AIHW 2014 concerning the overlap between CVD, CKD, and T2DM) the proportion of CKD patients not eligible under the T2DM restriction could be as low as 83.2% (see paragraph 6.61). This compares to 93.4% used in the submission estimates. In terms of the estimated savings, the PBAC agreed with the DUSC that savings associated with ESKD would be delayed but not avoided, and also noted that the impact for the Australian Government would need the impact for State/Territory Governments removed from the financial estimates. Overall, the PBAC considered that the financial impact was overestimated, but would remain high even once the eligible population was greatly reduced as per PBAC advice.
- 7.12 In addition, the PBAC recalled the DUSC's advice for the previous HFREF submission that that the risk of leakage is likely to be high as dapagliflozin is already well-known to prescribers and that there may also be an increase in patients utilising the diabetes restriction due to the positive outcomes for other diseases (paragraph 6.60,

dapagliflozin Public Summary Document, November 2020 PBAC meeting). The PBAC considered that this risk applied also to the CKD listing. Importantly, the PBAC also considered that the price reduction did not remove the overall uncertainties with the estimates, and it recommended that an RSA would be needed to manage the risk of an uncertain patient population. Finally, the PBAC considered that financial estimates for the dapagliflozin market across T2DM, HFREF and CKD were needed to inform its deliberations about how best to ensure that PBS subsidy be limited to only those patients in whom it had determined its use would be cost effective.

Outcome:

Deferred

Addendum to the July 2021 PBAC PSD:

**4.02 DAPAGLIFLOZIN,
Tablet 10 mg,
Forxiga[®],
AstraZeneca Pty Ltd**

8 Background

- 8.1 At its July 2021 meeting, the PBAC deferred its decision about the PBS listing of dapagliflozin for the treatment of patients with chronic kidney disease (CKD). The PBAC also deferred its decision with respect to a concurrent submission for dapagliflozin for heart failure with reduced ejection fraction (HFrEF). As noted in paragraph 7.1 above, the decision was deferred as the submission had estimated the overall net impact of the HFrEF and CKD listings, but had not provided estimates with respect to the existing T2DM indication. The PBAC had requested that the department obtain these estimates from the sponsor, as it “considered that financial estimates for the dapagliflozin market across T2DM, HFrEF and CKD were needed to inform its deliberations about how best to ensure that PBS subsidy be limited to only those patients in whom it had determined its use would be cost effective” (paragraph 7.12).
- 8.2 The department obtained additional information from the sponsor in August 2021, which the PBAC considered at its September 2021 meeting.
- 8.3 For the CKD submission, the PBAC had previously considered that there were several uncertainties with respect to the estimation of the eligible population, the estimation of the overlapping populations with T2DM and HFrEF, and the estimated net savings to government health budgets from ESKD delayed (paragraph 7.9). Overall, the PBAC considered that the financial impact for CKD presented in the July 2021 submission was overestimated, but would remain high even once the eligible population was reduced as per PBAC advice (paragraphs 7.10 and 7.11).

9 Consideration of the evidence

Revised CKD estimates

- 9.1 Compared to the July 2021 submission, the overall financial estimates presented by the sponsor were reduced (\$800 million to < \$900 million to \$500 million to < \$600 million over six years, see Table 20 below). This was in part due to the application of changes applied in the pre-PBAC response, which PBAC had previously considered reasonable (a revised lower DPMQ of \$██████, increased annual CKD diagnosis rate and treatment uptake, and application of a stopping rule).
- 9.2 Further changes made were:

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- A decrease in the estimated proportion of diagnosed CKD patients meeting the PBS restriction criteria in terms of eGFR and UACR (from 58% to 49%, based on CKD stage estimates used as proxies for the PBS criteria);
- A decrease in the overlapping population with T2DM (from 93.4% to 88.3%);
- Exclusion of patients with polycystic kidney disease, ANCA-associated vasculitis, and lupus nephritis;
- A decrease in the proportion of CKD patients not eligible for PBS-listed SGLT2 inhibitors for T2DM (HbA1c ≤7.0%), from 93.4% to 88.3%; and
- An increase in the proportion of CKD patients not eligible for PBS-listed dapagliflozin for HFrEF, from 97.4% to 97.7% (which was also previously applied in the pre-PBAC response).

9.3 Table 19 below outlines the methods and assumptions used in the financial estimates presented to PBAC in July 2021 and September 2021.

Table 19: Key inputs used in the financial estimates presented to PBAC in July 2021 and September 2021, for chronic kidney disease

Parameter	Value applied and source		PBAC view (as per section 11 Outcome)
	July 2021 submission	September 2021 estimates	
Australian adults (%) with biomedical data suggesting CKD	<p>Assumed prevalence of 10%, based on patient biomedical data (2011-12 NHMS) and KHA (2012) definition of CKD</p> <p>Year 1: 2,075,792 to Year 6: 2,239,310</p> <p>PBAC consideration: PBAC noted the NHMS did not review duration of CKD markers, and may have counted data unrelated to CKD (e.g. AKI, kidney/urogenital infection) (para 6.68).</p>	<p>Year 1: 2,075,792 to Year 6: 2,239,310</p> <p>Unchanged from the original submission and a likely overestimate.</p>	Reasonable, but highly uncertain
Adults (%) with biomedical data suggesting CKD, likely to be diagnosed with CKD	<p>Rate of diagnosis of 10% based on survey of self-reported kidney disease</p> <p>Year 1: 10% (2011-12 AHS)</p> <p>Assumed annual 2% increase to Year 6: 20%</p> <p>Number of patients: Year 1: 207,579 to Year 6: 447,862.</p> <p>Revised in the pre-PBAC response to annual 5% increase to Year 6: 35%.</p> <p>PBAC consideration: PBAC agreed with the DUSC that the diagnosis rate was likely underestimated, and considered that the adjustment made in the pre-PBAC response was appropriate (para 7.9).</p>	<p>Number of patients as per pre-PBAC response: Year 1: 207,579 to Year 6: 783,759</p>	Remained reasonable as aligned with DUSC advice that there is increasing screening and diagnosis of CKD in general practice.

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Parameter	Value applied and source		PBAC view (as per section 11 Outcome)
	July 2021 submission	September 2021 estimates	
Proportion of patients meeting the PBS criteria in terms of eGFR of 25–75 mL/min/1.73 m ² and a UACR of 200–5000 mg/g	<p>CKD stages 2-3b used as proxy. Assumed based on biomedical data (2011-12 NHMS)</p> <p>5.8% (sum of % undiagnosed CKD 2-3b) 58% (% of diagnosed CKD; 0.058 / 0.10)</p> <p>Number of patients: Year 1: 120,396 to Year 6: 259,760</p> <p>PBAC consideration: PBAC considered using CKD stage 2-3b only as a proxy for PBS population had vastly overestimated eligible patients (para 6.70).</p> <p>PBAC noted that in the NHMS, 6.7% were estimated to have microalbuminuria (males 2.5–25 mg/mmol and females 3.5–35 mg/mmol), and only 0.9% (males >25 mg/mmol and females >35 mg/mmol) were estimated to have macroalbuminuria. PBAC considered that very few patients with microalbuminuria were likely to meet the PBS eligibility criteria of 22.6–565 mg/mmol, and therefore the 5.8% used by the submission to determine eligibility was likely vastly overestimated (para 6.68).</p>	<p>CKD stages 3a and 3b used as proxy.</p> <p>Number of patients: Year 1: 101,734 to Year 6: 260,835</p> <p>The sponsor claimed that it did not identify relevant data to inform the assumptions for the proportion of patients with micro- or macroalbuminuria by disease stage.</p> <p>The proportion of CKD patients stages 3a and 3b was assumed to be 49%, based on an average of the proportion of patients in these stages across five data sources: the National Prescribing Service (NPS) MedicineWise’s MedicineInsight dataset (n=1.3 million); 2011-2012 NHMS; CKD Queensland Registry (n=1051); and two QLD registries (Mallett 2014, n=2935 and Mahmoud 2017, n=1265).</p> <p>In NHMS data only, the proportion of CKD patients with stages 3a and 3b was 33.3%, and the sponsor applied this value in a scenario analysis.</p>	<p>Remained very significantly overestimated; PBAC previously considered that the estimate would be closer to 0.9% than 5.8% of undiagnosed CKD; that is, closer to 9% than 58% of diagnosed.</p>
Patients with polycystic kidney disease, lupus nephritis and ANCA-associated vasculitis.	<p>Original financial estimates included these subpopulations.</p> <p>PBAC consideration: PBS restriction and estimates should also exclude: 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 (paras 7.3 and 7.10).</p>	<p>Excluded patients with polycystic kidney disease, lupus nephritis or ANCA-associated vasculitis. Based on Queensland registry data presented in Mallett et al 2014, assumed 94.34% of CKD patients do not have these conditions.</p>	<p>The applicability of Queensland data was unknown, and patients with a history of cytotoxic or immunosuppressive therapy for kidney disease, or an organ transplant had not been excluded. As the overall impact of further changes was likely to be small, these estimates were reasonable.</p>

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Parameter	Value applied and source		PBAC view (as per section 11 Outcome)
	July 2021 submission	September 2021 estimates	
Adults (%) with biomedical data suggesting CKD, with/without overlapping comorbidities of T2DM and/or CVD	<p>CKD only: 4.9% CKD + CVD: 3.5% CKD + T2DM: 0.6% CKD + CVD + T2DM: 1.1% (2011-12 AHS)</p> <p>Evaluation comments: 2011-2012 AHS data is the most recent reliable Australian data, but may not reflect current Australian setting. Estimates were based on older 2011-2012 biomedical data (NHMS 2013) and were highly uncertain (Table 17).</p>	Unchanged	Remained highly uncertain as based on older 2011-2012 data, although reasonable to use as this was the most recent reliable Australian data.
Proportion of CKD patients not eligible for PBS-listed SGLT2 inhibitors for T2DM (HbA1c ≤7.0%)	<p>93.4% based on following factors: Diabetics with T2DM: 88% (AUSDIAB 2012) T2DM eligible for SGLT2i: 44.4% (AUSDIAB 2012) Morbidity overlap CKD + T2DM: 0.6%; and CKD + CVD + T2DM: 1.1% (2011-12 AHS)</p> <p>PBAC consideration: Based on AIHW 2014 analysis of NHMS 2011-2012 data, could be as low as 83.2%, although the PBAC acknowledged that this estimate did not explicitly account for eligibility according to the existing and proposed PBS restrictions (para 6.61)</p>	Sponsor used a midpoint of 88.3% based on its original assumption of 93.4% and PBAC's suggested proportion of 83.2% (the latter was applied in a scenario analysis).	Remained a likely overestimate, but the revised value was more reasonable in the absence of alternative evidence.
Proportion of CKD patients not eligible for PBS-listed dapagliflozin for HFrEF	<p>97.4% based on the following factors: Adults with CVD: 22% (AIHW 2014) Adults with HF: 2.2% (Liew et al. 2020) HF likely to be HFrEF: 57% (SNAPSHOT-HF data) Morbidity overlap CKD + CVD: 3.5%; and CKD + CVD + T2DM: 1.1% (2011-12 AHS)</p> <p>Revised in the pre-PBAC response to 97.7%, by narrowing the CKD overlap with HFrEF patients (LVEF<40%) to those in NHYA Classes II-IV receiving SOC.</p>	As per pre-PBAC response.	Remained highly uncertain, but likely reasonable in the absence of alternative evidence.

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Parameter	Value applied and source		PBAC view (as per section 11 Outcome)
	July 2021 submission	September 2021 estimates	
Treatment adherence	98.6% for dapagliflozin and empagliflozin Evaluation comments: Derived from the DAPA-CKD trial. May not be applicable to clinical practice (Table 17).	Unchanged	May not be applicable to clinical practice. PBAC noted that adherence in DAPA-HF was 96.7%, but the HFrEF resubmission had applied adherence of 85% in its financial estimates (Table 12, 7.01 dapagliflozin PSD, July 2021 PBAC meeting). PBAC considered that there was no reason to expect that adherence for CKD would be higher.
Treatment utilisation			
Uptake of dapagliflozin	█% in Year 1 increasing to █% in Years 3-6. Increased in the pre-PBAC response. PBAC consideration: PBAC agreed with the DUSC that the uptake rate was likely underestimated, and considered that the adjustment made in the pre-PBAC response was appropriate (para 7.9).	Revised as per the pre-PBAC response, i.e.: Year 1-6= █%, █%, █%, █%, █%, █%.	Uncertain, although adjustments remained appropriate as they aligned with DUSC's advice that the submission had originally underestimated the uptake.
Proportion of patients with CKD taking SGLT2 inhibitors (SGLT2i) for T2DM	Assumed to be equivalent to the population excluded as eligible for SGLT2i therapies █% (█-█%) Assumed empagliflozin █%; dapagliflozin █%	Increased to █% (i.e. due to proportion ineligible being reduced from █% to █%). Market share split of █% empagliflozin and █% dapagliflozin was retained	Uncertain, but reasonable.
Empagliflozin users switching to dapagliflozin	█%	Assumption retained.	Uncertain assumption.

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Parameter	Value applied and source		PBAC view (as per section 11 Outcome)
	July 2021 submission	September 2021 estimates	
Proportion of patients who do not initiate RRT (i.e. application of a 'stopping rule')	<p>The original submission did not incorporate a stopping rule, however the pre-PBAC response did present an estimates scenario to account for a restriction criterion requiring discontinuation of treatment at initiation of renal replacement therapy (RRT; dialysis or transplant). The sponsor claimed that the proportions of patients discontinuing at RRT was derived from the economic model in section 3 of the submission. Proportions continuing were Yrs 1-6: [redacted]%, [redacted]%; [redacted]%; [redacted]%; [redacted]%; [redacted]%; [redacted]%</p> <p>PBAC consideration: The PBAC considered that it would be appropriate to cease treatment on commencement of RRT given the lack of evidence to support continued use in this population (para 7.4). The PBAC noted that although the pre-PBAC response had provided an appropriate scenario analysis, it was unclear how the proportion of discontinuing patients were derived, and this would need to be clarified in revised estimates obtained from the sponsor (para 7.9).</p>	<p>Stopping rule applied as per scenario analysis in pre-PBAC response.</p> <p>The sponsor explained that: - Firstly, the proportion of patients progressing to ESKD per year in the dapagliflozin and placebo arms was estimated from the time to ESKD Kaplan-Meier data with lognormal parametric extrapolation. - Secondly, the prevalence data of treated (receiving transplant or dialysis) and untreated ESKD (receiving conservative management) patients from the Australia and New Zealand Dialysis & Transplant Registry (ANZDATA) was applied to the proportion of patients progressing to ESKD to estimate the proportion of those patients receiving RRT.</p>	<p>Appropriate; additional explanation of method applied was satisfactory.</p>
ESKD savings	<p>Events and costs derived from the economic evaluation.</p> <p>PBAC consideration: The PBAC agreed with the DUSC that savings associated with ESKD would be delayed but not avoided, and also noted that the impact for the Australian Government would need the impact for State/Territory Governments removed from the financial estimates (para 7.11)</p>	<p>All ESKD savings removed from estimates</p>	<p>Excluding all ESKD savings was reasonable in the context of substantial uncertainty, the majority of savings accruing to State/Territory budgets, and because ESKD savings to all budgets would be mostly delayed, rather than avoided entirely.</p>

Source: Table 4.1.1, p134 and Table 4.2.1, p138 of the July 2021 dapagliflozin CKD submission; pre-PBAC response from July 2021; PBAC PSD from July 2021; Attachment 3 financial estimates model provided with the additional information in August 2021.
PSD: Public Summary Document

9.4 The table below presents a comparison of the financial estimates between the July 2021 submission and the additional information considered in September 2021 (excluding ESKD costs avoided in both cases). The estimated total patients increased from the original submission, but decreased from the pre-PBAC response (1,000,000 to < 2,000,000 compared with 700,000 to < 800,000 and 1,000,000 to < 2,000,000 respectively). The estimated financial impact decreased compared with both the

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original submission and the pre-PBAC response (\$500 million to < \$600 million compared with \$800 million to < \$900 million and \$700 million to < \$800 million respectively).

Table 20: Comparison of the financial estimates presented to the PBAC in July 2021 and September 2021

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	6-year total cost
Estimated total patients							
July 2021	1	2	3	3	3	3	
July 2021 prePBAC	2	3	3	4	5	6	
September 2021	7	3	3	3	4	5	
Scripts dispensed (13.045 scripts per year x 98.6% compliance for both July and September estimates)							
July 2021	8	9	9	9	9	10	
July 2021 prePBAC	9	9	10	11	12	13	
September 2021	14	9	9	10	11	11	
Cost to R/PBS (less copayments)							
July 2021 ^a	\$ 15	\$ 16	\$ 17	\$ 17	\$ 17	\$ 18	
July 2021 prePBAC ^b	\$ 19	\$ 20	\$ 17	\$ 17	\$ 17	\$ 18	
September 2021 ^c	\$ 21	\$ 22	\$ 20	\$ 17	\$ 17	\$ 17	
Net savings of empagliflozin (less copayments)							
July 2021 ^a	-\$ 23	-\$ 23	-\$ 23	-\$ 23	-\$ 23	-\$ 23	
July 2021 prePBAC ^b	-\$ 23	-\$ 23	-\$ 23	-\$ 23	-\$ 23	-\$ 23	
September 2021 ^c	-\$ 23	-\$ 23	-\$ 23	-\$ 23	-\$ 23	-\$ 23	
Net cost to R/PBS (less copayments)							
July 2021 ^a	\$ 15	\$ 16	\$ 17	\$ 17	\$ 17	\$ 17	\$ 24
July 2021 prePBAC ^b	\$ 19	\$ 15	\$ 17	\$ 17	\$ 17	\$ 18	\$ 25
September 2021 ^c	\$ 21	\$ 22	\$ 20	\$ 16	\$ 17	\$ 17	\$ 26

Source: Table 18, dapagliflozin, PSD, July 2021 PBAC meeting; Table 7, p19 of the additional information provided in August 2021.

^a Based on original proposed DPMQ of \$

^b Based on revised DPMQ of \$, price for the listing as at 1 June 2021.

^c Based on revised DPMQ \$, price for the listing as at 1 July 2021.

The redacted values correspond to the following ranges

- ¹150,000 to < 60,000
- ²80,000 to < 90,000
- ³100,000 to < 200,000
- ⁴200,000 to < 300,000
- ⁵300,000 to < 400,000
- ⁶400,000 to < 500,000
- ⁷60,000 to < 70,000
- ⁸700,000 to < 800,000
- ⁹1,000,000 to < 2,000,000
- ¹⁰2,000,000 to < 3,000,000
- ¹¹3,000,000 to < 4,000,000
- ¹²4,000,000 to < 5,000,000
- ¹³5,000,000 to < 6,000,000
- ¹⁴800,000 to < 900,000
- ¹⁵\$60 million to < \$70 million
- ¹⁶\$90 million to < \$100 million
- ¹⁷\$100 million to < \$200 million
- ¹⁸\$200 million to < \$300 million
- ¹⁹\$40 million to < \$50 million
- ²⁰\$70 million to < \$80 million
- ²¹\$30 million to < \$40 million
- ²²\$50 million to < \$60 million
- ²³\$0 to < \$10 million

²⁴\$800 million to < \$900 million

²⁵\$700 million to < \$800 million

²⁶\$500 million to < \$600 million

9.5 The sponsor also provided scenario analyses:

- **Scenario A:** using CKD stage 3a and 3b from the 2011-2012 NHMS dataset as a proxy for patients who meet the PBS restriction in terms of eGFR and UACR (33.3%, compared to 49% in revised estimates, and 58% in the July 2021 submission). The sponsor considered that this approach was conservative.
- **Scenario B:** assuming that the proportion of CKD patients not eligible for PBS-listed SGLTi for T2DM (HbA1c ≤7.0%) was 83.2%, compared with 88.3% in the revised estimates, and 93.4% in the July 2021 submission.

9.6 The scenarios resulted in a net financial impact to the R/PBS of \$300 million to < \$400 million and \$500 million to < \$600 million over six years, and are shown in the table below (700,000 to < 800,000 and 1,000,000 to < 2,000,000 patients respectively).

Table 21: Scenario analyses presented in September 2021

Estimated total patients	■ ¹	■ ²	■ ³	■ ³	■ ³	■ ⁴
Net cost to R/PBS (less copayments)	\$■ ⁵	\$■ ⁶	\$■ ⁷	\$■ ⁸	\$■ ⁹	\$■ ¹⁰
Estimated total patients	■ ¹¹	■ ¹²	■ ³	■ ³	■ ⁴	■ ⁴
Net cost to R/PBS (less copayments)	\$■ ⁶	\$■ ⁷	\$■ ⁸	\$■ ¹³	\$■ ¹⁰	\$■ ¹⁰

Source: Table 8, pp20-21 of the additional information provided in August 2021.

The redacted values correspond to the following ranges

¹140,000 to < 50,000

²70,000 to < 80,000

³100,000 to < 200,000

⁴200,000 to < 300,000

⁵\$20 million to < \$30 million

⁶\$30 million to < \$40 million

⁷\$40 million to < \$50 million

⁸\$60 million to < \$70 million

⁹\$80 million to < \$90 million

¹⁰\$100 million to < \$200 million

¹¹60,000 to < 70,000

¹²90,000 to < 100,000

¹³\$90 million to < \$100 million

Combined estimates for HFrEF, CKD and T2DM

9.7 The table below presents a summary of the revised estimates for the net impact of listing dapagliflozin HFrEF and CKD on the R/PBS, along with the estimated net impact for the current T2DM dapagliflozin listing. Estimates were also presented for the total SGLT2 inhibitor market. The sponsor noted that these estimates were based on a market share approach, and the analysis assumed no growth of the oral T2DM market would be attributable to the proposed HFrEF and CKD listings. The sponsor considered

this to be a conservative assumption as it claimed that a substantial proportion of T2DM patients are not treated optimally.

Table 22: Estimated net cost to R/PBS across currently listed and proposed dapagliflozin indications

Indication/s	Baseline (2020/2021)	2022	2023	2024	2025	2026	2027
Dapagliflozin market							
CKD	NA	\$ [redacted] ¹	\$ [redacted] ²	\$ [redacted] ³	\$ [redacted] ⁴	\$ [redacted] ⁵	\$ [redacted] ⁶
HFrEF	NA	\$ [redacted] ⁶	\$ [redacted] ⁷	\$ [redacted] ¹	\$ [redacted] ⁸	\$ [redacted] ²	\$ [redacted] ⁹
T2DM	\$ [redacted] ⁸	\$ [redacted] ⁵	\$ [redacted] ⁵	\$ [redacted] ⁵	\$ [redacted] ⁵	\$ [redacted] ¹⁰	\$ [redacted] ¹⁰
CKD +HFrEF	NA	\$ [redacted] ⁸	\$ [redacted] ³	\$ [redacted] ⁵	\$ [redacted] ⁵	\$ [redacted] ⁵	\$ [redacted] ¹⁰
CKD +HFrEF +T2DM	NA	\$ [redacted] ⁵	\$ [redacted] ¹⁰	\$ [redacted] ¹⁰	\$ [redacted] ¹¹	\$ [redacted] ¹²	\$ [redacted] ¹²
Total SGLT2i market							
T2DM	\$ [redacted] ⁵	\$ [redacted] ¹⁰	\$ [redacted] ¹⁰	\$ [redacted] ¹¹	\$ [redacted] ¹¹	\$ [redacted] ¹¹	\$ [redacted] ¹²
CKD +HFrEF +T2DM	NA	\$ [redacted] ¹⁰	\$ [redacted] ¹¹	\$ [redacted] ¹²	\$ [redacted] ¹²	\$ [redacted] ¹³	\$ [redacted] ¹⁴

Source: Table 1, p7, of the additional information provided in August 2021.

CKD, chronic kidney disease; HFrEF, heart failure with reduced ejection fraction; NA, not applicable; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme; SGLT2i, sodium-glucose co-transporter 2 inhibitor.

The redacted values correspond to the following ranges

¹\$30 million to < \$40 million

²\$50 million to < \$60 million

³\$70 million to < \$80 million

⁴\$90 million to < \$100 million

⁵\$100 million to < \$200 million

⁶\$10 million to < \$20 million

⁷\$20 million to < \$30 million

⁸\$40 million to < \$50 million

⁹\$60 million to < \$70 million

¹⁰\$200 million to < \$300 million

¹¹\$300 million to < \$400 million

¹²\$400 million to < \$500 million

¹³\$500 million to < \$600 million

¹⁴\$600 million to < \$700 million

9.8 The submission claimed that the estimates factored in:

- growth in the T2DM market due to:
 - population growth;
 - the ageing population;
 - the increase in risk factors for T2DM;
 - the ability for general practitioners to intervene in the management of T2DM sooner and at the point of care (e.g. with the upcoming MBS-listing of HbA1c point-of-care testing for the maintenance of T2DM management); and
 - increased awareness of treatment options.

- a shift in clinical management of patients with T2DM to a risk-based approach for patients who have risk factors for CV and renal complications based on recommendations by the three local T2DM guidelines: Living Evidence Guidelines in Diabetes, the Australian Diabetes Society (ADS) T2DM treatment guidelines, and the Royal Australian College of General Practitioners (RACGP) Australian type 2 diabetes management algorithm;
- higher uptake of dapagliflozin in eligible T2DM patients based on evidence of dapagliflozin in new indications (e.g. HFrEF and CKD), new TGA approved indications (e.g. dapagliflozin for HFrEF), and a potential impact of PBS listings in HFrEF and CKD; and
- higher rate of new initiations and switching of patients from treatment with a dipeptidyl peptidase-4 inhibitor to an SGLT2-I, particularly if the HbA1c is not controlled and the patient has CV risks.

Proposed Risk Sharing Arrangement

- 9.9 The sponsor claimed that given demonstrated cost-effectiveness across all three indications (HFrEF, CKD and T2DM), the certainty in the clinical data, and the PBS restrictions proposed for HFrEF and CKD, there was minimal overall risk of leakage into populations that have not been deemed cost-effective.
- 9.10 To minimise uncertainty, the sponsor proposed a [REDACTED] % rebate of PBS expenditure above the proposed expenditure caps. The proposed expenditure caps were based on the estimates for the combined HFrEF, CKD and T2DM expenditure in Table 22.
- 9.11 The sponsor emphasised that the proposed expenditure caps should represent a reasonable estimate of dapagliflozin utilisation, “without unduly impacting the net price when used in an appropriate patient population.” The sponsor therefore proposed that, if the PBAC were to recommend alternative estimates for the T2DM utilisation and expenditure, a [REDACTED] % rebate of expenditure above the caps should no longer be applied, “but rather a rebate that is representative of the CKD and HFrEF proportion of expenditure.”

10 Revised requested listing

- 10.1 The sponsor noted various amendments recommended by the PBAC in terms of the proposed restriction (paragraphs 3.1-3.8, 7.3-7.4), and presented a revised restriction. The sponsor’s additions to the section 3 ‘Requested listing’ of the July 2021 PBAC Public Summary Document (PSD) are shown in italics and deletions in strikethrough. The Secretariat noted some minor refinements would be needed for additional clarity.

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
DAPAGLIFLOZIN					
dapagliflozin 10 mg tablet, 28	TBC	1	28	5	Forxiga
Restriction Summary [new] / Treatment of Concept: [new]					
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required – Streamlined [new code]					
Indication: Chronic kidney disease					
Treatment Phase:					
Clinical criteria:					
<i>Patient must have a diagnosis of chronic kidney disease, defined as abnormalities of kidney structure or function present for 3 months or more, prior to initiating treatment with this drug,</i>					
AND					
Clinical criteria:					
<i>Patient must have an estimated glomerular filtration rate of between 25 and 75 mL/min/1.73 m² inclusive, to substantiate the diagnosis of kidney disease, prior to initiating treatment with this drug,</i>					
AND					
Clinical criteria:					
<i>Patient must have a urinary albumin to creatinine ratio of between 200 and 5000 mg/g (22.6–565 mg/mmol) inclusive, to substantiate the diagnosis of kidney disease, prior to initiating treatment with this drug,</i>					
AND					
Clinical criteria:					
<i>Patient must not progress to end-stage renal disease defined as an estimated glomerular filtration rate (eGFR) of less than 15 mL/min/1.73 m² while on this drug; discontinue treatment with this drug prior to initiating renal replacement therapy, defined as dialysis or kidney transplant,</i>					
AND					
Clinical criteria:					
<i>Patient must receive treatment in combination with the maximum tolerated dose of an ACE inhibitor; or</i>					
<i>Patient must receive treatment in combination with the maximum tolerated dose of an angiotensin II receptor antagonist unless medically contraindicated to these classes of drug,</i>					
AND					
Clinical criteria:					
<i>Patient must not be receiving treatment with another sodium-glucose co-transporter 2 (SGLT2) inhibitor.</i>					
Prescribing instructions:					
<i>Patient must be stabilised on either (i) an ACE inhibitor or (ii) an angiotensin II receptor antagonist for a period of 4 weeks, unless medically contraindicated, prior to initiation of combination therapy with this drug.</i>					
Prescribing instructions:					
<i>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.</i>					
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.					

11 PBAC Outcome

- 11.1 The PBAC did not recommended extending the existing listing of dapagliflozin to include a General Schedule Authority Required (Streamlined) listing for the treatment of patients with chronic kidney disease (CKD). The PBAC reiterated that it was satisfied that dapagliflozin added to standard care provides, for some patients, a significant improvement in efficacy over standard care alone. The PBAC remained of the view that the listing would be cost-effective at the price proposed in the pre-PBAC response from July 2021 (the [REDACTED] price for dapagliflozin for [REDACTED]). However, the revised financial estimates remained high and uncertain, and did not form a reliable basis for a risk-sharing arrangement with the Australian Government.
- 11.2 The PBAC reiterated its previous views with respect to: the high and urgent unmet need for effective treatments for CKD; the appropriateness of the comparator; the trial evidence; and the lack of robust economic modelling; and the restriction (see section 7 above). The PBAC clarified that it considered that the high and urgent unmet need related to the fact that there are limited effective therapies on the PBS for this life-threatening condition, although it also noted that most patients are expected to progress over a number of years.
- 11.3 In terms of the financial estimates previously presented, the PBAC recalled it had considered that:
- Several uncertainties existed including the estimation of the eligible population, the estimation of the overlapping populations with T2DM and HFrEF, and the estimated net savings to government health budgets from ESKD delayed.
 - Increases to uptake and diagnosis rates as per the pre-PBAC response were appropriate and aligned with DUSC advice. A ‘stopping rule’ would also be appropriate as per the pre-PBAC response scenario analysis, but clarification of the method applied was needed.
 - The eligible population had been very significantly overestimated;
 - The estimates may have included patients with reversible kidney disease or reversible clinical factors affecting kidney function, and would have included other groups to be excluded in the restriction;
 - ESKD savings were highly uncertain, and the majority of savings would accrue to State/Territory Governments and would need to be removed from the estimated impact on the Australian Government;
 - The risk of leakage was high as dapagliflozin was well known to prescribers, and there may be an increase in patients using the diabetes restriction due to positive outcomes for other diseases.
- 11.4 The PBAC noted the revised CKD estimates from the sponsor, and expressed a view with respect to each parameter (shown in Table 19). Critically, the proportion of

patients meeting the PBS restriction in terms of eGFR and UACR remained very significantly overestimated.

- 11.5 The PBAC also noted the revised estimates with respect to the T2DM population and considered that substantial uncertainties remained. The PBAC noted that the sponsor stated that the T2DM estimates assumed no growth of the oral T2DM would be attributable to the proposed HFrEF and CKD listings; that is, it claimed that all additional use for dapagliflozin would be due to substitution within the existing oral T2DM market. The PBAC considered that the assumed growth rates in the T2DM market were inadequately justified, and likely substantially overestimated. The substantial growth assumption also seemed counter to the assumption that there would be no growth due to listings for HFrEF and CKD. Therefore, the estimates were not considered a reliable basis for informing a broad RSA for dapagliflozin.
- 11.6 The PBAC also noted that the sponsor had proposed an RSA across HFrEF, CKD and T2DM, with a [REDACTED] % rebate above the expenditure caps. The sponsor also noted that if the PBAC were to recommend alternative estimates for the T2DM utilisation and expenditure, a [REDACTED] % rebate of expenditure above the caps should no longer be applied, “but rather a rebate that is representative of the CKD and HFrEF proportion of expenditure.” As the PBAC considered that neither the T2DM nor the CKD estimates formed a reliable basis for an RSA, it only recommended a listing for HFrEF (discussed in item 4.03, dapagliflozin for HFrEF, September 2021 PBAC meeting).
- 11.7 In the context of high uncertainty, and high overall R/PBS impact even once estimates were reduced as per PBAC advice, the PBAC reiterated that an RSA was essential for ensuring that subsidy was only provided to patients in whom the PBAC had determined dapagliflozin use would be cost-effective. The inflated estimates presented by the sponsor provided no protection against use in patients outside the CKD restriction (e.g. in patients meeting the eGFR criteria but not the UACR criteria, to whom there was a high risk of leakage).
- 11.8 The PBAC noted that a standard re-entry pathway was available to the sponsor. The PBAC considered a resubmission for dapagliflozin for CKD should address the following issues:
- Better define the proportion of patients meeting the PBS criteria in terms of eGFR and UACR. The PBAC considered the estimates which informed the base case (58%) and scenario analysis (33.3%) to be over-estimates.
 - Reduce the treatment adherence from 98.6% to approximately 85%.
- 11.9 The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.
- 11.10 In terms of the requested restriction, the PBAC recognised that the sponsor had addressed its main concerns, but noted the Secretariat’s advice that some additional refinement may be appropriate in order to improve clarity.

11.11 The PBAC noted that this submission is not eligible for an Independent Review.

Outcome:

Not recommended

12 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.

13 Sponsor's Comment

The sponsor had no comment.

Addendum to the September 2021 PBAC PSD:

**3.01 DAPAGLIFLOZIN,
Tablet 10 mg,
Forxiga[®],
AstraZeneca Pty Ltd**

14 Background

14.1 Additional information was provided by the sponsor that was considered at the November 2021 PBAC. The following inputs to the financial estimates were revised since the PBAC’s consideration at the September 2021 Intracycle meeting:

- Proportion of patients meeting estimated glomerular filtration rate (eGFR) and urinary albumin to creatinine ratio (uACR) criteria: This estimate had been reduced based on an additional proportion of macroalbuminuria applied to the proportion of patients diagnosed with CKD meeting the eGFR criteria (23.7%).
- Overlapping population with T2DM eligible for an SGLT2-I under current T2DM listings: This was reduced to the proportion proposed by the PBAC (83.2%).
- The revised estimates assumed a higher diagnosis rate.

14.2 Table 23 below compares the methods and assumptions used in the financial estimates presented to PBAC in September and November 2021 (see Table 19 for a comparison between the July and September 2021 methods and assumptions). Table 23 only covers parameters that determine the number of eligible patients as these were the ones considered most critical by the PBAC.

Table 23: Key inputs used in the financial estimates presented to PBAC in September 2021 and November 2021, for chronic kidney disease

Parameter	Value applied and source		PBAC view
	September 2021 estimates	November 2021 estimates	
Australian adults (%) with biomedical data suggesting CKD	Assumed prevalence of 10%, based on patient biomedical data (2011-12 NHMS) and KHA (2012) definition of CKD Year 1: 2,075,792 to Year 6: 2,239,310 PBAC consideration: Reasonable, but highly uncertain	Year 1: 2,075,792 to Year 6: 2,239,310 Unchanged.	Assumption considered reasonable by PBAC. 2,075,792 in 2022 is reasonably consistent with the 1,712,500 from the 2011-12 AHS.

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Parameter	Value applied and source		PBAC view
	September 2021 estimates	November 2021 estimates	
Adults (%) with biomedical data suggesting CKD, likely to be diagnosed with CKD	<p>Rate of diagnosis of 10% based on survey of self-reported kidney disease Year 1: 10% (2011-12 AHS) Assumed annual 5% increase to Year 6: 35% Number of patients: Year 1: 207,579 to Year 6: 783,759.</p> <p>PBAC consideration: Reasonable as aligned with DUSC advice that there is increasing screening and diagnosis of CKD in general practice</p>	<p>Year 1: 10%, assumed annual 10% increase to Year 6: 60% Number of patients: Year 1: 207,579 to Year 6: 1,343,586</p> <p>Sensitivity analysis: Unchanged</p>	<p>PBAC suggested a rate of 50% for Year 1, increasing by 5% per year over the forward estimates.</p>
Proportion of patients meeting the PBS criteria in terms of eGFR of 25–75 mL/min/1.73 m ² and a uACR of 200–5000 mg/g	<p>CKD stages 3a and 3b used as proxy. Number of patients: Year 1: 101,734 to Year 6: 260,835</p> <p>The sponsor claimed that it did not identify relevant data to inform the assumptions for the proportion of patients with micro- or macroalbuminuria by disease stage.</p> <p>The proportion of CKD patients stages 3a and 3b was assumed to be 49%, based on an average of the proportion of patients in these stages across five data sources: the National Prescribing Service (NPS) MedicineWise’s MedicineInsight dataset (n=1.3 million); 2011-2012 NHMS; CKD Queensland Registry (n=1051); and two QLD registries (Mallett 2014, n=2935 and Mahmoud 2017, n=1265).</p> <p>In NHMS data only, the proportion of CKD patients with stages 3a and 3b was 33.3%, and the sponsor applied this value in a scenario analysis.</p> <p>PBAC Consideration: Remained very significantly overestimated; PBAC previously considered that that the estimate would be closer to 0.9% than 5.8% of undiagnosed CKD; that is, closer to 9% than 58% of diagnosed.</p>	<p>Reduced from 49.01% to 23.70% Assuming that 49.01% of patients are Stage 3a or 3b and of these 48.3% are estimated to have macroalbuminuria.</p> <p>Number of patients: Year 1: 49,112 to Year 6: 317,885</p>	<p>The PBAC considered that 7.5% of the diagnosed population would be eligible based on the UACR criterion in the restriction (≥ 200 and ≤ 5000 mg/g) (AHS 2011, Ausdiab 1999) and 33% would be eligible based on the eGFR criterion (≥ 25 to ≤ 75 mL/min/1.73 m²) (AHS 2011 CKD stages 3a-3b). As the UACR criterion is the more restrictive, this parameter was estimated to be 7.5% by the PBAC.</p>
Proportion of CKD patients on stable ACE-I or ARB	100%	100%	80%

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Parameter	Value applied and source		PBAC view
	September 2021 estimates	November 2021 estimates	
Patients with polycystic kidney disease, lupus nephritis and ANCA-associated vasculitis.	<p>Excluded patients with polycystic kidney disease, lupus nephritis or ANCA-associated vasculitis. Based on Queensland registry data presented in Mallett et al 2014, assumed 94.34% of CKD patients do not have these conditions.</p> <p>PBAC Consideration: The applicability of Queensland data was unknown, and patients with a history of cytotoxic or immunosuppressive therapy for kidney disease, or an organ transplant had not been excluded. As the overall impact of further changes was likely to be small, these estimates were reasonable.</p>	Unchanged	
Adults (%) with biomedical data suggesting CKD, with/without overlapping comorbidities of T2DM and/or CVD	<p>CKD only: 4.9% CKD + CVD: 3.5% CKD + T2DM: 0.6% CKD + CVD + T2DM: 1.1% (2011-12 AHS)</p> <p>Unchanged from July 2021 estimates</p>	Unchanged	
Proportion of CKD patients not eligible for PBS-listed SGLT2 inhibitors for T2DM (HbA1c ≤7.0%)	<p>Sponsor used a midpoint of 88.3% based on its original assumption of 93.4% and PBAC's suggested proportion of 83.2% (the latter was applied in a scenario analysis).</p> <p>PBAC Consideration: Remained a likely overestimate, but the revised value was more reasonable in the absence of alternative evidence.</p>	Reduced to 83.20% .	PBAC suggested a rate of 50% based on the ANZDATA Registry data ¹ where close to 50% of Australian patients in 2019 had Type 2 diabetes on initiation of renal replacement therapy (RRT). PBAC further noted in the pivotal trial (DAPA CKD) that 67.6% of patients had T2DM at baseline.
Proportion of CKD patients not eligible for PBS-listed dapagliflozin for HFrEF	<p>Proportion increased slightly compared to the original submission from 97.4% to 97.7% by narrowing the CKD overlap with HFrEF patients (LVEF<40%) to those in NHYA Classes II-IV receiving SOC.</p> <p>PBAC Consideration: Remained highly uncertain, but likely reasonable in the absence of alternative evidence.</p>	Unchanged	PBAC suggested a rate of 90% based on the pivotal trial (DAPA CKD) where 10.9% of patients had HF at baseline.

¹https://www.anzdata.org.au/wp-content/uploads/2020/09/c01_incidence_2019_ar_2020_v1.0_20201111.pdf

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Parameter	Value applied and source		PBAC view
	September 2021 estimates	November 2021 estimates	
Proportion of patients who do not initiate RRT (i.e. application of a 'stopping rule')	<p>99% Stopping rule applied as per scenario analysis in pre-PBAC response.</p> <p>The sponsor explained that: - Firstly, the proportion of patients progressing to ESKD per year in the dapagliflozin and placebo arms was estimated from the time to ESKD Kaplan-Meier data with lognormal parametric extrapolation. - Secondly, the prevalence data of treated (receiving transplant or dialysis) and untreated ESKD (receiving conservative management) patients from the Australia and New Zealand Dialysis & Transplant Registry (ANZDATA) was applied to the proportion of patients progressing to ESKD to estimate the proportion of those patients receiving RRT.</p> <p>PBAC Consideration: Appropriate; additional explanation of the method applied was considered satisfactory.</p>	Unchanged	

Application of the parameters in Table 23 gives an overall eligibility rate of 1.8% (37,275 patients) using the November 2021 sponsor estimates and 1.25% (21,406 patients) using the PBAC suggested parameters (see Table 24). The PBAC noted that the difference in the utilisation of dapagliflozin estimated by the sponsor compared to the PBAC was further magnified with the application of increasing diagnosis rates over the forward estimates.

Table 24: Summary of November 2021 Sponsor estimates and PBAC estimates

Parameter	November 2021 estimates	PBAC estimate
Adults (%) with biomedical data suggesting CKD, likely to be diagnosed with CKD	10%	50%
Proportion of patients meeting the PBS criteria in terms of eGFR of 25–75 mL/min/1.73 m ² and a UACR of 200–5000 mg/g	23.66%	7.5%
Proportion of CKD patients on stable ACE-I or ARB	100%	80%
Proportion of CKD patients not eligible for PBS-listed SGLT2 inhibitors for T2DM (HbA1c ≤7.0%)	83.2%	50%
Proportion of CKD patients not eligible for PBS-listed dapagliflozin for HFrEF	97.67%	90%
Proportion of patients who do not initiate RRT	99%	99%
Patients with polycystic kidney disease, lupus nephritis and ANCA-associated vasculitis.	94.34%	94.34%
Overall % eligible (of adults with biomedical data suggesting CKD)	1.80%	1.25%
Number eligible patients (in 2022 based on 2,075,792 patients with biomedical data suggesting CKD)	37,275	21,406

15 PBAC Outcome

- 15.1 The PBAC did not recommend extending the existing listing of dapagliflozin to include a General Schedule Authority Required (Streamlined) listing for the treatment of patients with chronic kidney disease (CKD). The PBAC reiterated that it was satisfied that dapagliflozin added to standard care provides, for some patients, a significant improvement in efficacy over standard care alone. The PBAC remained of the view that the listing would be cost-effective at the price proposed in the pre-PBAC response from July 2021 (the [REDACTED] price for dapagliflozin for [REDACTED]). However, the revised financial estimates remained high and uncertain, and did not form a reliable basis for a risk-sharing arrangement (RSA) with the Australian Government.
- 15.2 The PBAC considered that the number of eligible patients remained overestimated in the Sponsor's November 2021 estimates which estimated for Year 1 that 1.80% of adults with biomedical data suggesting CKD would be eligible compared to the PBAC estimate of 1.25%. This means the number of eligible patients was around 44% higher in the Sponsor's estimates than based on the PBAC assumptions.
- 15.3 The PBAC remained concerned there was a high risk of use outside the proposed restriction in patients with low-grade proteinuria for whom the benefit from treatment with dapagliflozin has not been demonstrated (or claimed by the sponsor).
- 15.4 The PBAC considered that the outstanding issues could be easily resolved in a simple resubmission for dapagliflozin using the early re-entry pathway. If the sponsor accepts this pathway, the following changes to the utilisation estimates may address these outstanding issues without requiring further re-evaluation:
- Increasing the proportion of patients diagnosed with CKD in Year 1 from 10% to 50%, and applying a 5% annual increase in the diagnosis rate from Year 2 to Year 6. i.e. Year 1 50%, Year 2, 55%, Year 3 60%, Year 4 65%, Year 5 70% and Year 6 75%.
 - Reducing the proportion of patients meeting the PBS criteria in terms of eGFR of 25–75 mL/min/1.73 m² and a UACR of 200–5000 mg/g from 23.70% to 7.5%.
 - Reducing the proportion of CKD patients on stable ACE-I or ARB from 100% to 80%.
 - Reducing the proportion of CKD patients not eligible for PBS-listed SGLT2 inhibitors for T2DM (HbA1c ≤7.0%) from 83.2% to 50.0%.
 - Reducing the proportion of CKD patients not eligible for PBS-listed dapagliflozin for HFrEF from 97.67% to 90%.

The resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early re-entry timing is not acceptable, a standard re-entry pathway is available.

15.5 The PBAC noted that this submission is not eligible for an Independent Review.

Outcome:

Not recommended

16 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.

17 Sponsor's Comment

The sponsor had no comment.