An addendum to these minutes has been included at the end of the document.

7.01 DAPAGLIFLOZIN, Tablet 10 mg, Forxiga®, AstraZeneca Pty Ltd

1 Purpose of submission

1.1 The standard re-entry resubmission requested an Authority Required (Streamlined) General Schedule listing of dapagliflozin for the treatment of patients with symptomatic heart failure with reduced ejection fraction (HFrEF), who are receiving concomitant optimal standard chronic heart failure treatment which includes (unless contraindicated or not tolerated) a beta-blocker and an angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker (ARB) or angiotensin receptor neprilysin inhibitor (ARNI).

1.2 A submission for dapagliflozin for HFrEF was considered at the November 2020 PBAC meeting. A concurrent submission for dapagliflozin for the treatment of chronic kidney disease (CKD) was considered at the July 2021 PBAC meeting (item 6.03 refers). The resubmission 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. The estimated distribution and impact of existing and proposed concurrent dapagliflozin PBS listings were discussed in Section 5 of the Commentary, and key details are presented under the Additional Information heading below.

1.3 Listing was requested on the basis of a cost-effectiveness analysis for dapagliflozin plus standard care versus standard care alone.

Table 1: Key components of the clinical issue addressed in the resubmission

Component	Description
Population	Patients with symptomatic (NYHA Class II-IV) chronic heart failure with reduced ejection fraction who are receiving (unless contraindicated or not tolerated): a beta-blocker; an ACE inhibitor, ARB or sacubitril/valsartan; and, if appropriate, an MRA.
Intervention	Dapagliflozin 10 mg once daily added to standard care comprising: a beta-blocker; an ACE inhibitor, ARB or sacubitril/valsartan; and, if appropriate, an MRA.
Comparator	Standard of care alone (main comparator), defined as: - a beta-blocker plus an ACE inhibitor or ARB (+/- an MRA and other heart failure medications) for the majority of patients (80-89%); and - a beta-blocker plus an ARNI (+/- an MRA and other heart failure medications) for a minor proportion of patients (11-20%). Empagliflozin plus standard care (potential near market comparator)
Outcomes	Time to hospitalisation for heart failure; time to urgent heart failure visit; time to cardiovascular death; death; time to death from any cause; heart failure-related quality of life; safety.
Clinical claim	When used in the management of patients with HFrEF, dapagliflozin added to standard care comprising a beta-blocker plus an ACE inhibitor, ARB, or ARNI (and, if appropriate, an MRA) is: - superior in terms of effectiveness and non-inferior in terms of safety compared to standard care alone comprising a beta-blocker plus an ACE inhibitor, ARB or ARNI (and, if appropriate, an MRA); - non-inferior in terms of effectiveness compared to empagliflozin plus standard care.*

Source: Table 1.1-1, pp32-33 of the resubmission.
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.
Underlined text indicates key changes from the November 2020 submission.
** This reference was provided with the clinical comparison in the supplementary analysis of the submission, which did not explicitly claim non-inferiority to empagliflozin, but rather was a clinical comparison provided for completeness (see para 6.11).*

2 Background

Registration status

2.1 Dapagliflozin was registered on the Australian Register of Therapeutic Goods on 5 November 2020 for use in adults for the treatment of symptomatic heart failure with reduced ejection fraction, as an adjunct to standard of care therapy.

2.2 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.

2.3 Dapagliflozin for the treatment of adult patients with CKD was also under review by TGA at the time of this submission.

Previous PBAC consideration

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addresses it
Main comparator	The PBAC considered that the appropriate comparator for the majority of dapagliflozin use would be 'standard of care' consisting of an ACE inhibitor (or ARB) and a beta-blocker (paragraph 7.4, dapagliflozin, PSD, November 2020 PBAC meeting). The PBAC considered that 'standard of care plus sacubitril/valsartan' (i.e., a beta-blocker plus sacubitril/valsartan) would be an appropriate comparator for a minor proportion of the proposed population. The PBAC considered that this portion could be reasonably estimated as somewhere between 11% and 20% (paragraph 7.5, dapagliflozin, PSD, November 2020 PBAC meeting).	Addressed. The resubmission nominated standard care as the main comparator, defined as a beta-blocker plus an ACE inhibitor or ARB (with or without an MRA and other heart failure medications) for the majority of patients (80-89%); and a beta-blocker plus an ARNI (with or without an MRA and other heart failure medications) for a minor proportion of patients (11-20%).
Clinical place in therapy	The PBAC considered that dapagliflozin has a different mechanism of action compared to sacubitril/valsartan, and patients will potentially switch from, add-on, or displace sacubitril/valsartan, or grow the current heart failure market (paragraph 7.3, dapagliflozin, PSD, November 2020 PBAC meeting).	Addressed. The resubmission positioned dapagliflozin as an add-on therapy for patients treated with standard care that includes a beta blocker; and an ACE inhibitor, ARB or ARNI. Switching between an ARNI and dapagliflozin was not considered in the economic evaluation or financial estimates. No new or updated treatment guidelines were identified in the resubmission.
Economic analysis	The PBAC considered the cost effectiveness of dapagliflozin added to standard care (comprising a beta-blocker plus an ACE inhibitor or ARB) versus standard care alone (comprising a beta-blocker plus an ACE inhibitor or ARB) would need to be established in a future resubmission. The PBAC considered that an additional cost-effectiveness analysis would also be required for concomitant use of dapagliflozin and sacubitril/valsartan (plus a beta-blocker) compared to sacubitril/valsartan (plus a beta-blocker), which would be allowed under the proposed PBS listing (paragraph 7.1, dapagliflozin, PSD, November 2020 PBAC meeting).	Addressed. The resubmission presented a modelled economic evaluation for dapagliflozin plus standard care versus placebo plus standard care, in patients with HFrEF. The base-case results of the model comprised a weighted-average of the results for patients receiving a beta-blocker plus an ACE inhibitor or ARB (89.3%); and patients receiving a beta-blocker plus an ARNI (10.7%), based on the distribution of ARNI use in the DAPA-HF trial.
Financial estimates	The PBAC noted the DUSC's advice that the financial estimates were likely underestimated and agreed that there were a number of issues including a high risk of leakage in earlier stages of disease, underestimated uptake rates, and a lack of accounting for concomitant use of dapagliflozin and sacubitril/valsartan (paragraph 7.12, dapagliflozin, PSD, November 2020 PBAC meeting).	Addressed. The resubmission updated the epidemiological inputs, dapagliflozin uptake rates, and compliance assumptions used to derive the financial impacts. PBS and MBS cost offsets associated with displaced sacubitril/valsartan prescriptions included in the November 2020 submission were removed from the budget impact estimates.

Component	Matter of concern	How the resubmission addresses it
Quality use of medicines	The PBAC expressed concern around the QUM issues raised in the evaluation and by DUSC, noting that these were not identified or addressed in the submission (paragraph 7.12, dapagliflozin, PSD, November 2020 PBAC meeting).	Addressed. The resubmission provided expert opinion to address the QUM issues raised in relation to the November 2020 dapagliflozin submission. The resubmission also provided a list of current and future activities to support the quality use of medicines in relation to dapagliflozin for the treatment of HFrEF.
Risk sharing arrangement	The PBAC rejected the submission's proposal to share the caps of the current risk-sharing arrangement for sacubitril/valsartan, considering that a separate and distinct RSA for dapagliflozin would be required (paragraph 7.13, dapagliflozin, PSD, November 2020 PBAC meeting).	No risk-sharing arrangements were proposed in the current resubmission.

Source: Dapagliflozin, Public Summary Document, November 2020 PBAC meeting, and the dapagliflozin resubmission to the July 2021 PBAC meeting.

ACE, angiotensin-converting enzyme; ARNI, angiotensin receptor neprilysin inhibitor; ARB, angiotensin II receptor blocker; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; PSD, Public Summary Document; QUM, quality use of medicines.

2.4 The pre-PBAC response reiterated the sponsor's view that the PBAC had established a precedent for acceptable cost effectiveness for new treatments in this patient population in its recommendation to list sacubitril/valsartan for this indication. The sponsor was concerned that an appropriate frame of reference had not been taken into consideration during the evaluation of dapagliflozin for HFrEF. The PBAC noted this comment but recalled its previous view that sacubitril/valsartan and dapagliflozin are likely to be used differently in clinical practice. (paragraph 7.2, dapagliflozin Public Summary Document (PSD), November 2020 PBAC meeting).

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

3 Requested listing

3.1 The requested restriction was the same as proposed in the November 2020 submission (apart from the addition of previous Secretariat suggestions and deletions). In the table below, further additions proposed by the Secretariat and ESC are added in italics and suggested deletions are crossed out with strikethrough.

MEDICINAL PRODUCT medicinal product pack	**Max. qty packs**	**Max. qty units**	**№.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: ☒ Medical Practitioners ☒ Nurse practitioners
	Restriction type: ☒ Authority Required (STREAMLINED) [new code]
	Indication: Chronic heart failure
	Treatment Phase: [blank]
	Clinical criteria:
	Patient must be symptomatic with NYHA classes II, III or IV,
	AND
	Clinical criteria:
	Patient must have a documented left ventricular ejection fraction (LVEF) of less than or equal to 40%,
	AND
	Clinical criteria:
	Patient must receive concomitant optimal standard chronic heart failure treatment, which must include the maximum tolerated dose of a beta-blocker, unless contraindicated or not tolerated;
	AND
	Clinical criteria:
	~~Patient must be receiving treatment with an ACE inhibitor,~~ *Patient must receive treatment in combination with the maximum tolerated dose of an ACE inhibitor,* unless contraindicated according to the TGA-approved Product Information or cannot be tolerated; or
	~~Patient must be receiving treatment with an angiotensin II antagonist,~~ *Patient must receive treatment in combination with the maximum tolerated dose of an angiotensin II antagonist,* unless contraindicated according to the TGA-approved Product Information or cannot be tolerated; or
	~~Patient must be receiving treatment with an angiotensin receptor with neprilysin inhibitor combination therapy~~ *Patient must receive treatment in combination with the maximum tolerated dose of an angiotensin receptor with neprilysin inhibitor combination therapy,* unless contraindicated according to the TGA-approved Product Information or cannot be tolerated,
	AND
	Clinical criteria:
	Patient must not be receiving treatment with another sodium-glucose co-transporter 2 (SGLT2) inhibitor.
	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 resubmission requested a DPMQ of $[redacted]. The requested DPMQ was lower than the proposed price of $[redacted] included in the November 2020 pre-PBAC response, which was calculated by weighting the existing price in T2DM ([redacted]%) and a heart failure price derived from cost-minimisation of dapagliflozin to the sacubitril/valsartan published price less the cost of valsartan ([redacted]%).

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 the proportional use across T2DM ($56.85),

CKD ($[redacted]) and HFrEF ($[redacted]) indications. A proposed weighted price was not provided in the submission, but was included in the Pre-Sub-Committee Response (PSCR) ($[redacted] for HF and T2DM, $[redacted] for HF, T2DM and CKD). 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 $[redacted], to align with the [redacted] price. At the time of the PBAC meeting, the T2DM price was $[redacted].

3.4 The requested restriction was narrower than the TGA indication, but broadly consistent with the DAPA-HF trial (the key clinical evidence in the resubmission).

3.5 There is a risk of use outside of the proposed restriction among patients with heart failure with preserved ejection fraction, patients with heart failure with midrange ejection fraction, patients with NYHA Class I heart failure, and patients who are not receiving optimal therapy with a beta-blocker and an ACE inhibitor, ARB, or ARNI.

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

4 Population and disease

4.1 Chronic heart failure is a complex clinical syndrome characterised by symptoms such as dyspnoea, peripheral oedema and fatigue, caused by an underlying structural and/or functional cardiac abnormality that impairs the ability of the heart ventricle to fill with or eject blood. Common causes of heart failure include ischaemic heart disease, valvular heart disease, cardiomyopathies, hypertension, arrhythmias, and diabetes.

4.2 Heart failure is commonly classified based on the left ventricular ejection fraction (LVEF). Heart failure with reduced ejection fraction (HFrEF) refers to symptoms with or without signs of heart failure and a left ventricular ejection fraction ≤40%. If LVEF is mildly reduced (41-49%), additional criteria are required for diagnosis (signs of heart failure, diastolic dysfunction with high filling pressure demonstrated by invasive means or echocardiography or biomarker testing).

4.3 Liew et al. (2020) estimated that there were almost 420,000 adults in Australia with heart failure in 2017, representing 2.2% of the adult population. The prevalence of heart failure in Indigenous Australians is estimated to be 1.7 times that of non-Indigenous Australians (Woods et al., 2012). Heart failure mortality studies estimate 3 and 4-year survival rates for HFrEF of 32% and 41%, respectively (Somaratne et al., 2009; Meta-analysis Global Group in Chronic Heart Failure., 2012).

4.4 Dapagliflozin is a selective inhibitor of sodium-glucose co-transporter 2 (SGLT2). The specific mechanisms underlying the benefits of dapagliflozin in heart failure are unclear.

4.5 The previous submission had stated that dapagliflozin was an alternative or add-on option to sacubitril/valsartan (an ARNI), although the cost-effectiveness of dapagliflozin as add-on therapy to sacubitril/valsartan was not examined in that

submission (paragraphs 3.5 and 4.6, dapagliflozin PSD, November 2020 PBAC meeting). The PBAC previously considered that the clinical place for dapagliflozin was unclear and likely to evolve. In addition, the PBAC considered that dapagliflozin has a different mechanism of action compared to sacubitril/valsartan, and patients will potentially switch from, add-on, or displace sacubitril/valsartan, or grow the current heart failure market (paragraphs 7.1 and 7.3, dapagliflozin PSD, November 2020 PBAC meeting). The resubmission positioned dapagliflozin as an add-on therapy for patients treated with standard care that includes a beta blocker and an ACE inhibitor, ARB or ARNI. Switching between an ARNI and dapagliflozin was not considered in the economic evaluation or financial estimates of the resubmission.

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

5 Comparator

5.1 The resubmission nominated standard care as the main comparator, defined as:

- a beta-blocker plus an ACE inhibitor or ARB (with or without an MRA and other heart failure medications) for the majority of patients (80-89%); and
- a beta-blocker plus an ARNI (with or without an MRA and other heart failure medications) for a minor proportion of patients (11-20%).

5.2 This ESC considered this was reasonable. The PBAC previously considered that the appropriate comparator for the majority of dapagliflozin use would be 'standard of care' consisting of an ACE inhibitor (or ARB) and a beta-blocker. The PBAC stated that MRAs and other background heart failure therapies could be considered as part of this standard of care, but noting the variability of individualised care, the PBAC viewed that they would complicate a cost-effectiveness comparison and could potentially be excluded if their financial impact were minor (paragraph 7.4, dapagliflozin, PSD, November 2020 PBAC meeting).

5.3 The PBAC previously considered that 'standard of care plus sacubitril/valsartan' (i.e., a beta-blocker plus sacubitril/valsartan) would be an appropriate comparator for a minor proportion of the proposed population and that this portion could be reasonably estimated as somewhere between 11% (the proportion in the DAPA-HF trial using both dapagliflozin and sacubitril/valsartan at baseline) and 20% (the proportion of concomitant use estimated in the PSCR and pre-PBAC response, based on the EMPEROR-Reduced trial and clinical opinion; paragraph 7.5, dapagliflozin, PSD, November 2020 PBAC meeting).

5.4 The resubmission identified empagliflozin as a potential near market comparator, noting that the results of a Phase III trial of empagliflozin in patients with HFrEF (EMPEROR-Reduced) have been published since the November 2020 submission. The TGA received an application for evaluation of empagliflozin for the treatment of heart failure in January 2021.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (14) and organisations (4) via the Consumer Comments facility on the PBS website. Comments were received from the Centre for Community-Driven Research, Diabetes Australia, hearts4heart, and the National Aboriginal Community Controlled Health Organisation. The comments described a range of benefits of treatment with dapagliflozin including reduced hospitalisations, reduced cardiovascular deaths and improved quality of life. The comments also described: the challenges with currently available treatment (in terms of dosing and adherence); the known long-term safety profile of dapagliflozin with respect to its use in T2DM; and the clinical needs of specific populations including Aboriginal and Torres Strait Islander patients and those with T2DM. The comments also noted the increasing recognition of SGLT2 inhibitors in international treatment guidelines for heart failure, including in the Canadian Cardiovascular Society/ Canadian Heart Failure Society Guidelines Update (April 2021) and the 2021 Update to the 2017 American College of Cardiology Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment (February 2021).

Clinical trials

6.3 The resubmission included the following comparisons:

- A head-to-head comparison of dapagliflozin plus standard care versus placebo plus standard care in patients with symptomatic HFrEF (DAPA-HF trial). The DAPA-HF trial was previously considered by PBAC at the November 2020 PBAC meeting.
- An indirect comparison of dapagliflozin plus standard care (DAPA-HF trial) versus empagliflozin plus standard care (EMPEROR-Reduced trial), using placebo plus standard care as common reference. The PBAC did not formally review this comparison given no submission for empagliflozin had been received.

6.4 Details of the trials presented in the resubmission are provided in the table below.

Table 3: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
DAPA-HF	Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF).	Clinical Study Report, October 2019.
	McMurray JJV, DeMets DL, Inzucchi SE, et al. The Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) trial: baseline characteristics.	*Eur J Heart Fail*. 2019; 21(11): 1402-1411.
	McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction.	*NEJM* 2019; 381(21): 1995-2008.

Trial ID	Protocol title/ Publication title	Publication citation
	McMurray JJV, DeMets DL, Inzucchi SE, et al. A trial to evaluate the effect of the sodium-glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF).	*Eur J Heart Fail*. 2019; 21(5): 665-675.
	Berg DD, Jhund PS, Docherty KF, et al. Time to clinical benefit of dapagliflozin and significance of prior heart failure hospitalization in patients with heart failure with reduced ejection fraction.	*JAMA Cardiol*. 2021; doi: 10.1001/jamacardio.2020.7585.
	Dewan P, Docherty KF, Bengtsson O, et al. Effects of dapagliflozin in heart failure with reduced ejection fraction, and COPD: An analysis of DAPA-HF.	*Eur J Heart Fail*. 2020; doi: 10.1002/ejhf.2083.
	Dewan P, Solomon SD, Jhund PS, et al. Efficacy and safety of sodium–glucose co-transporter 2 inhibition according to left ventricular ejection fraction in DAPA-HF.	*Eur J Heart Fail*. 2020; 22(7): 1247-1258.
	Docherty KF, Jhund PS, Anand I, et al. Effect of dapagliflozin on outpatient worsening of patients with heart failure and reduced ejection fraction: A prespecified analysis of DAPA-HF.	*Circulation* 2020; 142(17): 1623-1632.
	Docherty KF, Jhund PS, Bengtsson O, et al. Effect of dapagliflozin in DAPA-HF according to background glucose-lowering therapy.	*Diabetes Care* 2020; 43(11): 2878-2881.
	Docherty KF, Jhund PS, Inzucchi SE, et al. Effects of dapagliflozin in DAPA-HF according to background heart failure therapy.	*Eur Heart J.* 2020; 41(25): 2379-2392.
	Inzucchi SE, Docherty KF, Køber L, et al. Dapagliflozin and the incidence of Type 2 diabetes in patients with heart failure and reduced ejection fraction: an exploratory analysis from DAPA-HF.	*Diabetes Care* 2020; 44(2): 586-594.
	Jackson AM, Dewan P, Anand IS, et al. Dapagliflozin and diuretic use in patients with heart failure and reduced ejection fraction in DAPA-HF.	*Circulation* 2020; 142(11): 1040-1054.
	Jhund PS, Solomon SD, Docherty KF, et al. Efficacy of dapagliflozin on renal function and outcomes in patients with heart failure with reduced ejection fraction: results of DAPA-HF.	*Circulation* 2020; 143(4): 298-309
	Kosiborod MN, Jhund PS, Docherty KF, et al. Effects of dapagliflozin on symptoms, function, and quality of life in patients with heart failure and reduced ejection fraction: results from the DAPA-HF trial.	*Circulation* 2020; 141(2): 90-99.
	Martinez FA, Serenelli M, Nicolau JC, et al. Efficacy and safety of dapagliflozin in heart failure with reduced ejection fraction according to age: insights from DAPA-HF.	*Circulation* 2020; 141(2): 100-111.
	Nassif ME, Windsor S, Tang F, et al. Dapagliflozin effects on biomarkers, symptoms, and functional status in patients with heart failure with reduced ejection fraction.	*Circulation* 2019; 140(18): 1463-1476.
	Petrie MC, Verma S, Docherty KF, et al. Effect of dapagliflozin on worsening heart failure and cardiovascular death in patients with heart failure with and without diabetes.	*JAMA* 2020; 323(14): 1353-1368.
	Serenelli M, Böhm M, Inzucchi SE, et al. Effect of dapagliflozin according to baseline systolic blood pressure in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure trial (DAPA-HF).	*Eur Heart J.* 2020; 41(36): 3402-3418.
	Solomon SD, Jhund PS, Claggett BL, et al. Effect of dapagliflozin in patients with HFrEF treated with sacubitril/valsartan: The DAPA-HF Trial. JACC:	*JACC: Heart Fail*. 2020; 8(10): 811-818.

Trial ID	Protocol title/ Publication title	Publication citation
	Sullivan K, Van Spall HGC. Dapagliflozin reduced worsening HF or CV death in HF with reduced ejection fraction.	*Ann Int Med* 2020; 172(4): JC16.
EMPEROR-Reduced	Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure.	*NEJM* 2020; 383(15): 1413-1424.
	Packer M, Butler J, Filippatos GS, et al. Evaluation of the effect of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality of patients with chronic heart failure and a reduced ejection fraction: rationale for and design of the EMPEROR-Reduced trial.	*Eur J Heart Fail*. 2019; 21(10): 1270-1278.
	Packer M, Anker SD, Butler J, et al. Influence of neprilysin inhibition on the efficacy and safety of empagliflozin in patients with chronic heart failure and a reduced ejection fraction: the EMPEROR-Reduced trial.	*Eur Heart J.* 2021; 42(6): 671-680.
	Anker SD, Butler J, Filippatos G, et al. Effect of empagliflozin on cardiovascular and renal outcomes in patients with heart failure by baseline diabetes status - results from the EMPEROR-Reduced trial.	*Circulation* 2020; 143(4): 337-349.
	Butler J, Anker SD, Filippatos G, et al. Empagliflozin and health-related quality of life outcomes in patients with heart failure with reduced ejection fraction: the EMPEROR-Reduced trial.	*Eur Heart J*. 2021; 42(13): 1203-1212.
	Packer M. Effect of empagliflozin on major heart failure outcomes, renal function and quality of life in patients with heart failure with a reduced ejection fraction, with and without sacubitril/valsartan.	*J Card Fail.* 2020; 26(12): 1109.
	Packer M, Anker SD, Butler J, et al. Effect of empagliflozin on the clinical stability of patients with heart failure and a reduced ejection fraction: the EMPEROR-Reduced trial.	*Circulation* 2021; 143: 326-336.
	Packer M, Butler J, Filippatos G, et al. Design of a prospective patient-level pooled analysis of two parallel trials of empagliflozin in patients with established heart failure.	*Eur J Heart Fail*. 2020; 22(12): 2393-2398.
	Zannad F, Ferreira JP, Pocock SJ, et al. Cardiac and kidney benefits of empagliflozin in heart failure across the spectrum of kidney function: insights from the EMPEROR-Reduced trial.	*Circulation* 2021; 143(4): 310-321.

Source: Table 2.2-1, pp65-67 of the resubmission; Table 2.2-1, p2 of Attachment 2.7 of the resubmission.
Selected citations relating to conference abstracts omitted.

6.5 The key features of the included trials are summarised in the table below.

Table 4: Key features of the included trials

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Dapagliflozin + standard care vs placebo + standard care						
DAPA-HF	4744	Phase 3, MC, parallel-group, R, DB, placebo-controlled (median duration of follow-up 18.2 months)	Low	• Age ≥18 years with symptomatic HFrEF • LVEF ≤40% • NYHA Class II-IV • Elevated NT-proBNP[1] • On background therapy with an ACE inhibitor (or ARB or sacubitril/valsartan), a beta-blocker; and an MRA (if considered appropriate)	• Time to CV death, hospitalisation for HF, or urgent HF visit (primary) • Time to CV death or hospitalisation for HF • CV death or recurrent HF hospitalisations • Time to ≥50% decline in eGFR, ESRD or renal death • Time to death from any cause • Change in KCCQ-TSS • Change in EQ-5D-5L	• Time to CV death and time to death from any cause used to model mortality transitions • Baseline EQ-5D-5L utility score used to model health state utilities
Empagliflozin + standard care vs placebo + standard care						
EMPEROR-Reduced	3730	Phase 3, MC, parallel-group, R, DB, placebo-controlled (median duration of follow-up 16 months)	Low	• Age ≥18 years with symptomatic HFrEF • LVEF ≤40% • NYHA Class II-IV • Elevated NT-proBNP[2] • Appropriate dose of medical therapy for HF (such as ACE inhibitor, ARB, beta-blocker, oral diuretics, MRA, ARNI, ivabradine) consistent with local and international guidelines	• Time to CV death or hospitalisation for HF (primary) • Time to hospitalisation for HF • Time to cardiovascular death • Total hospitalisations for HF • Change in slope of eGFR • Time to death from any cause • Change in KCCQ-CSS	-

Source: Section 2.3.1, pp69-70; Table 2.4-1, pp77-81; Table 2.4-8, pp90-93 of the resubmission; Table 2.6-3, p14; Table 2.6-5, pp16-18 of Attachment 2.7 of the resubmission.

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CSS, clinical summary score; CV, cardiovascular; DB, double blind; eGFR, estimated GFR; ESRD, end-stage renal disease; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MC, multi-centre; NT-proBNP N-Terminal pro b natriuretic peptide; NYHA, New York Heart Association; R, randomised; TSS, total symptom score.

[1] NT-proBNP ≥600 pg/mL (or if hospitalised for heart failure within the previous 12 months, NT-proBNP ≥400 pg/mL) at enrolment; or ≥900 pg/mL (irrespective of history of HF hospitalisation) if concomitant atrial fibrillation or atrial flutter (AF) at Visit 1.

[2] At least one of the following: 1) If ejection fraction (EF) ≥36% to ≤40%: elevated NT-proBNP at Visit 1 ≥2500 pg/mL for patients without AF, or ≥5000 pg/mL for patients with AF; 2) If EF ≥31% to ≤35%: elevated NT-proBNP at Visit 1 ≥1000 pg/mL for patients without AF, or ≥2000 pg/mL for patients with AF; 3) If EF≤30%: elevated NT-proBNP at Visit 1 ≥600 pg/mL for patients without AF, or ≥1200 pg/mL for patients with AF.

6.6 Baseline characteristics were generally well matched between treatment arms of the DAPA-HF trial. The trial population had a mean age of 66 years and included predominantly male patients (77%). Forty five percent of patients had T2DM. Based on the NYHA functional classification, 68% had Class II, 32% had Class III, and 1% had Class IV heart failure. The main aetiology of heart failure was ischaemic in 56.4% of patients and patients had a mean LVEF of 31.1%. At the time of randomisation, 56.1% of patients were receiving treatment with an ACE inhibitor; 27.6% with an ARB; 10.7% with an ARNI (93.6% with an ACE inhibitor, ARB or ARNI); 96.1% with a beta-blocker; 71.0% with an MRA; and 93.4% with a diuretic.

Comparative effectiveness

6.7 Results for the DAPA-HF trial were unchanged from the November 2020 submission (summarised in the table below).

Table 5: Results for the DAPA-HF trial primary and secondary outcomes based on the hierarchical testing sequence

	Dapagliflozin + SOC (N=2373)	Placebo + SOC (N=2371)	Comparison ratio[1] (95% CI)
Median duration of follow-up, months	18.3 (0.0-27.3)	18.2 (0.2-27.8)	
Composite of time to CV death, hospitalisation for HF or urgent HF visit, events n (%)	386 (16.3)	502 (21.2)	**0.74 (0.65, 0.85)**
Composite of time CV death or hospitalisation for HF, n (%)	382 (16.1)	495 (20.9)	**0.75 (0.65, 0.85)**
Composite of CV death or recurrent HF hospitalisation, n	567	742	**0.75 (0.65, 0.88)**
Change in the KCCQ-TSS at 8 months, mean change (SD)[2]	6.1 (18.6)	3.3 (19.2)	**1.18 (1.11, 1.26)**
Composite of time to ≥50% sustained decline in eGFR, ESRD or renal death, n (%)	28 (1.2)	39 (1.6)	0.71 (0.44, 1.16)
Time to death from any cause, n (%)	276 (11.6)	329 (13.9)	0.83 (0.71, 0.97)

Bolded result indicates statistically significant difference. The hierarchical testing sequence stopped prior to the outcome of time to death from any cause being assessed.

Source: Table 2.5-1, p.98 of the resubmission; Table 2, p6 of McMurray et al. (2019).

CI, confidence interval; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; ESRD, end-stage renal disease; SD, standard deviation; SOC, standard care; TSS, total symptom score.

[1] Hazard ratio for time to event outcomes; rate ratio for composite of CV death or recurrent HF; win ratio for change in the KCCQ-TSS at 8 months.

[2] Scored on a scale from 0 to 100, with a higher score indicating fewer symptoms and a change of 5 or more points considered to be clinically meaningful.

6.8 Based on the hierarchical testing sequence, treatment with dapagliflozin was associated with a statistically significant improvement in the primary composite endpoint of time to cardiovascular death, hospitalisation for heart failure or urgent heart failure visit; the composite of time to cardiovascular death or hospitalisation for heart failure; the composite of cardiovascular death or recurrent heart failure hospitalisation; and the change in the Kansas City Cardiomyopathy Questionnaire total symptom score, compared to placebo. There was no statistically significant difference in the composite of time to ≥50% sustained decline in eGFR, end-stage renal disease or renal death. The hierarchical testing sequence stopped prior to the outcome of time to death from any cause being assessed.

6.9 The benefit of dapagliflozin on the composite of cardiovascular death or heart failure events was generally consistent across pre-specified subgroups, including patients without T2DM. However, subgroup analysis suggested that dapagliflozin may be less effective relative to placebo in patients with NYHA Class III or IV heart failure. The ESC was of the view that initially after listing, the magnitude of benefit in the PBS population was likely to be less than that seen in the DAPA-HF as patients with more severe disease are treated with a newly accessible regimen. However, the ESC expected that over time, the PBS population would more closely reflect the trial population in terms of disease severity defined by NYHA Class.

6.10 The resubmission presented the results of indirect comparisons for dapagliflozin plus standard care versus empagliflozin plus standard care for the composite outcome of time to cardiovascular death or hospitalisation for heart failure, and the individual

outcomes of time to hospitalisation for heart failure, time to cardiovascular death, and time to death from any cause. There were no statistically significant differences for any of the presented indirect comparisons.

6.11 The resubmission claimed that the results for each of the indirect treatment comparisons were consistent with non-inferiority between dapagliflozin plus standard care and empagliflozin plus standard care. However, the results of the indirect comparisons should be interpreted with caution due to differences between the DAPA-HF and EMPEROR-Reduced trial in inclusion criteria, patient characteristics, standard care treatments, and trial follow-up durations. Additionally, no non-inferiority margins were proposed in the current resubmission. The ESC considered the analysis had been a prudent inclusion in the submission as a potential near market comparator, but noted that it was not relevant for PBAC decision-making regarding dapagliflozin at the present time.

Comparative harms

6.12 Table 6 summarises the results of safety outcomes for the DAPA-HF trial. These were unchanged from the previous submission.

Table 6: Summary of key adverse events in the DAPA-HF trial (on-treatment period)

AE category	Dapagliflozin + SOC (N=2368)	Placebo + SOC (N=2368)
Median duration of follow-up, months (range)	18.3 (0.0-27.3)	18.2 (0.2-27.8)
AE leading to death, n (%)	227 (9.6)	250 (10.6)
AE leading to dose interruption, n (%)	284 (12.0)	349 (14.7)
AE leading to dose reduction, n (%)	43 (1.8)	25 (1.1)
AE leading to discontinuation, n (%)	111 (4.7)	116 (4.9)
Serious AE, n (%)	846 (35.7)	951 (40.2)
Serious AE in >1%, n (%)		
- Cardiac failure	238 (10.1)	325 (13.7)
- Pneumonia	70 (3.0)	73 (3.1)
- Cardiac failure: congestive	57 (2.4)	65 (2.7)
- Cardiac failure: acute	36 (1.5)	51 (2.2)
- Death	33 (1.4)	38 (1.6)
- Acute myocardial infarction	32 (1.4)	32 (1.4)
- Ventricular tachycardia	32 (1.4)	53 (2.2)
- Cardiac failure chronic	24 (1.0)	26 (1.1)
- Ischaemic stroke	24 (1.0)	24 (1.0)
- Atrial fibrillation	23 (1.0)	37 (1.6)
- Angina unstable	21 (0.9)	29 (1.2)
- Acute kidney injury	20 (0.8)	41 (1.7)
- Sudden cardiac death	17 (0.7)	27 (1.1)
Adverse event of special interest, n (%)		
- Definite or probable diabetic ketoacidosis[1]	3 (0.1)	0
- Major hypoglycaemic event[2]	4 (0.2)	4 (0.2)
- AE suggestive of volume depletion	170 (7.2)	153 (6.5)
- Fracture	48 (2.0)	47 (2.0)
- Renal AE[3]	141 (6.0)	158 (6.7)
- Amputation[4]	11 (0.5)	11 (0.5)

Source: Table 2.5-7, p110; Table 2.5-8, pp111-112 of the resubmission.

AE, adverse event; SOC, standard of care.

[1] Events adjudicated as definite or probable diabetic ketoacidosis.

[2] AE with the following criteria confirmed by the investigator: i) symptoms of severe impairment in consciousness or behaviour; ii) need of external assistance; iii) intervention to treat hypoglycaemia; iv) prompt recovery of acute symptoms following the intervention.
[3] Based on pre-defined list of preferred terms.
[4] Surgical or spontaneous/non-surgical amputation, excluding amputation due to trauma.

6.13 Adverse events leading to discontinuation, and adverse events leading to death were similar between the dapagliflozin and placebo arms. Serious adverse events were numerically higher in the placebo arm compared to the dapagliflozin arm. The most common serious adverse events across both treatment arms were cardiac failure, pneumonia, and cardiac failure: congestive. The difference in serious adverse events between treatment arms appeared to be driven by heart failure-related adverse events (cardiac failure, cardiac failure: congestive, cardiac failure: acute).

6.14 Rates of adverse events of special interest, including major hypoglycaemic events, were generally similar between treatment arms, although adverse events suggestive of volume depletion were numerically higher in the dapagliflozin arm (7.2% versus 6.5%). Results for treatment-emergent adverse events and adverse events based on treatment grades were not included as outcomes for the DAPA-HF trial, and therefore no comparison across these outcomes could be made.

Benefits/harms

6.15 On the basis of the direct evidence presented in the resubmission, for every 100 patients treated with dapagliflozin plus standard care in comparison with placebo plus standard care for a median of 18 months:

- Approximately 5 fewer patients would die due to cardiovascular causes, be hospitalised for heart failure, or require an urgent heart failure visit resulting in intravenous therapy for heart failure. The difference was predominantly due to fewer heart failure hospitalisations.
- Approximately 5 fewer patients would experience a serious adverse event.

Clinical claim

6.16 The resubmission described dapagliflozin plus standard care as superior in terms of comparative effectiveness, and non-inferior in terms of safety, compared with standard care alone.

6.17 The PBAC previously considered that it was reasonable to claim superior comparative effectiveness of dapagliflozin added to standard care (comprising an ACE inhibitor, ARB, or sacubitril/valsartan; a beta-blocker; and, if appropriate, an MRA), compared to standard care alone (comprising an ACE inhibitor, ARB or sacubitril/valsartan; a beta-blocker; and, if appropriate, an MRA). The PBAC considered that the submission's claim of non-inferior safety was probably reasonable, although predominantly due to fewer heart failure events in the dapagliflozin arm, due to its superior efficacy over standard care (paragraph 6.47, dapagliflozin, PSD, November 2020 PBAC meeting). In July 2021, the PBAC reaffirmed these views regarding the clinical claims made in the resubmission.

6.18 The resubmission described dapagliflozin plus standard care as non-inferior in terms of effectiveness[1] compared to empagliflozin plus standard care. The resubmission claimed that differences in adverse event data collected between the DAPA-HF trial and the EMPEROR-Reduced trial, and differences in the durations of follow-up between the trials, meant that no robust conclusion regarding comparative safety for dapagliflozin plus standard care and empagliflozin plus standard care could be made.

Economic analysis

6.19 The resubmission presented a modelled economic evaluation of dapagliflozin plus standard care versus standard care alone, in patients with HFrEF. The economic analysis was based on the results of the DAPA-HF trial, with additional modelled data. The type of economic evaluation presented was a cost-utility analysis.

Table 7: Key components of the economic evaluation

Component	Description
Type of analysis	Cost-utility analysis
Outcomes	Life-years gained; quality-adjusted life years.
Time horizon	30 years in the model base case versus median follow-up of 18.2 months in the DAPA-HF trial.
Methods used to generate results	Markov state transition model (no half-cycle correction).
Treatments	Dapagliflozin plus standard care; placebo plus standard care.[1]
Health states	Two health states: 'alive'; 'dead'.
Cycle length	1 year
Transition probabilities	Transition probabilities for cardiovascular death and non-cardiovascular death based on data from the DAPA-HF trial, extrapolated over the time horizon using general population mortality rates (2018 Australian General Record of Incidence of Mortality data).
Health state utilities	DAPA-HF baseline utility with age-related decline based on Australian population utilities reported by Hawthorne et al. (2013). Included disutility associated with heart failure hospitalisation reported by Adena et al. (2019).

Source: Table 3.4-2, pp148-149 of the resubmission.

[1] Standard care comprising a beta-blocker plus an ACE inhibitor or ARB in 89.3% of patients and a beta-blocker plus an ARNI in 10.7% of patients.

6.20 The model was based on two health states ('alive' and 'dead'). All patients begin in the alive health state. Each cycle, patients could either stay alive, experience a cardiovascular death and transition to the dead state, or experience a non-cardiovascular death and transition to the dead state. Patients in the alive state could also experience a hospitalisation for heart failure each cycle. The ESC noted that hospitalisations for heart failure were associated with a cost and a disutility but did not alter the health state to which subjects moved in the subsequent cycle, and did not affect mortality rates. The ESC considered that there would be mortality impacts associated with continual re-admissions to hospital, as well as declining utility and increases in ongoing costs. On the whole, the ESC considered that the model structure

[1] *This reference was provided with the clinical comparison in the supplementary analysis of the submission, which did not explicitly claim non-inferiority to empagliflozin, but rather was a clinical comparison provided for completeness (see para 6.11).*

was overly simplistic as it did not adequately reflect the progressive nature of heart failure, and associated changes in costs, quality of life and mortality risk.

6.21 The PSCR argued that having more health states would have substantially increased uncertainty, and reiterated a claim that some published cost-effectiveness models in HFrEF used a two-state Markov model. The ESC noted economic models assessing the cost-effectiveness of dapagliflozin included in recent submissions to NICE and CADTH incorporated health states based on KCCQ-TSS and NYHA Class, respectively. The sponsor's claim that including additional health states would have significantly increased uncertainty was not considered reasonable.

6.22 The ESC recalled that it had previously considered that the two-state model structure included in the March 2016 sacubitril/valsartan submission did not accurately reflect disease progression through hospitalisation and rehospitalisation and through different NYHA functional classes of heart failure and did not reflect the progressive nature of heart failure. The PBAC previously agreed with the ESC that the failure of the model to better reflect disease progression meant that it was unlikely to be reliable for estimating incremental cost-effectiveness (paragraphs 6.30 and 7.9, sacubitril/valsartan, PSD, March 2016 PBAC meeting). The model structure was unchanged in the subsequent resubmission for sacubitril/valsartan, but the listing was accepted in the context of a reduced price, revised estimates and an RSA (Addendum to the sacubitril/valsartan PSD, July 2016 PBAC meeting).

6.23 The base case analysis utilised a 30-year time horizon with a 12-month cycle length. The ESC considered that the 12-month cycle length may to be too long to accurately capture outcome events and associated changes in resource use and health state utility for the HFrEF population. Additionally, half-cycle correction was not applied in the model. The lack of half-cycle correction was likely to have favoured the dapagliflozin arm due to the long cycle length and the application of transition probabilities at the end of each cycle (given improved survival associated with dapagliflozin treatment). Based on the PBAC Guidelines, half-cycle correction is the default approach to representing time of transition between states.

6.24 The model was based on the characteristics of patients in the DAPA-HF trial (mean age 66 years; 77% male; NYHA Class II: 68%; NYHA Class III: 32%; NYHA Class IV: 1%; T2DM: 45.1%; ARNI as part of background treatment: 10.7%). The resubmission presented a comparison of the DAPA-HF population with the populations included in six Australian heart failure studies. The resubmission argued that it was difficult to draw any conclusions regarding comparability given key differences between the DAPA-HF trial population and the populations included in the Australian heart failure studies, as well as heterogeneity across the Australian studies. In general, patients in the Australian studies appeared to be older, with a higher proportion of female patients. The evaluation considered the applicability of the modelled results to the proposed PBS population was unclear due to likely differences between the DAPA-HF trial population and the PBS population, including substantial differences in age, overall health status, the proportion of patients with T2DM, and the proportion of patients receiving treatment with an ARNI. The pre-PBAC response argued there was

no evidence of substantial differences in age between the DAPA-HF trial and the PBS population. It claimed that the sponsor's Australian patient familiarisation program (N=1,409) showed that the average age of patients initiated on dapagliflozin for HFrEF was similar to that in the DAPA-HF trial at 68 and 66 years, respectively. The PBAC noted that the ESC had reviewed Table 3.4-6 of the resubmission, which showed that the mean age of patients in some large Australian studies ranged from approximately 74 to 80 years, and the median recorded in other studies was from 72 to 80 years. The pre-PBAC response presented a sensitivity analysis with a starting age in the model of 75 years, which resulted in an ICER of $15,000 to < $25,000 per QALY saved (compared to $15,000 to < $25,000 in the base case).

6.25 The model provided the option of stratifying patients by the presence/absence of an ARNI as part of standard care treatment, or by the presence/absence of T2DM. The base-case model results were stratified according to ARNI use as part of standard care treatment, based on the proportion of patients receiving an ARNI at baseline in the DAPA-HF trial (i.e., beta-blocker plus an ACE inhibitor or ARB for 89.3%; beta-blocker plus an ARNI for 10.7%).

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

Table 8: Key drivers of the model

Description	Method/Value	Impact
Cardiovascular and non-cardiovascular mortality	The model incorporated cardiovascular and non-cardiovascular mortality based on the results of the DAPA-HF trial. Rates reported for the DAPA-HF trial were converted to transition probabilities and applied in the first year of the model (i.e., Cycle 1). Non-cardiovascular mortality was derived by deducting the cardiovascular mortality rate from the reported all-cause mortality rate. Transition probabilities beyond the first year of the model were derived by applying expected age-related cardiovascular and non-cardiovascular mortality increases to the trial-based transition probabilities used in Cycle 1. Age-related changes in the probabilities of cardiovascular and non-cardiovascular mortality were estimated from 2008 General Record of Incidence of Mortality (GRIM) data published by the AIHW. It was unclear whether the derived transitions adequately captured underlying mortality risk over time among the modelled HFrEF population. The applicability of the general population mortality estimates to increases in mortality over time in the HFrEF population was unclear, and the resubmission did not adequately justify the validity of the approach. The resubmission did not present data from published studies to validate the resulting mortality estimates.	Moderate, favours dapagliflozin
Dapagliflozin treatment effect	The model assumed that the treatment effect of dapagliflozin (based on a median duration of follow-up of 18.2 months in the DAPA-HF trial) in reducing cardiovascular and non-cardiovascular mortality, and in reducing heart failure hospitalisations, was maintained over the full duration of the model. The PSCR stated that transition probabilities from Cycle 1 of the model were drawn from DAPA-HF, and that from Cycle 2 onwards, transition probabilities increased according to expected age-related trends, using Australian mortality data. Thus, it claimed that the treatment effect of dapagliflozin was only assumed for one year. The ESC noted that the method used to derive transition probabilities from Cycle 2 onwards resulted in application of trial-based treatment effects for the full model time horizon, as was evident from inspection of the transition probabilities applied to each treatment arm from Cycle 2 onwards. This assumption was not adequately justified and was considered uncertain given the lack of long-term clinical data. The pre-PBAC response reiterated that there was no rationale to assume a waning treatment effect of dapagliflozin over time. It also argued that survival in both the dapagliflozin and placebo groups in the model were equally short (about 16 years), suggesting that the modelled benefits of dapagliflozin were not sustained. Furthermore, the pre-PBAC response presented sensitivity analyses assuming that the efficacy of dapagliflozin waned over time, such that the risks of both mortality and hospitalisations for HFrEF approached those of placebo in a linear fashion over 30 years and 15 years; the ICERs were, respectively, $[redacted][1] and $[redacted][2] per QALY saved (compared to the base case of $[redacted][1]).	High, favours dapagliflozin
Dapagliflozin treatment persistence	The model incorporated dapagliflozin treatment persistence based on drug discontinuation data reported in the DAPA-HF trial (based on the proportion of patients remaining on dapagliflozin after exclusion of deaths). A log-normal parametric function was used to extrapolate discontinuation data over the full duration of the model. The resubmission applied treatment persistence as a reduction in drug costs only. This was inappropriate, given that treatment persistence would also affect the effectiveness and safety of the treatment. Longer-term extrapolation of discontinuation rates was considered uncertain due to the relatively short duration of trial data (median 18.2 months follow-up) compared to the model time horizon (30 years).	Low, favours dapagliflozin

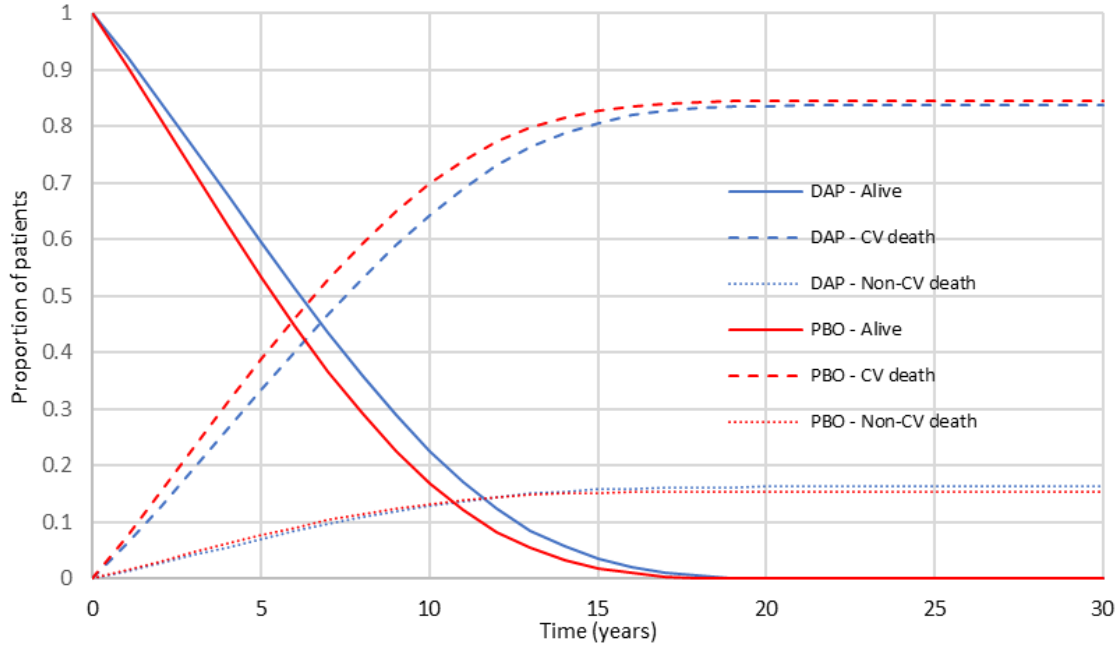
Description	Method/Value	Impact
Disease management costs	Annual non-hospitalisation costs were based on the median heart failure 'community costs' reported by Scuffham et al. (2017). Community costs included costs for allied health visits, GP visits (one health assessment and one care management plan per patient per annum), nursing home/aged care, and pharmaceuticals (estimated from the PBS drug costs multiplied by duration of use). The reported median cost of $3,000 was inflated to a 2022 value of $3,256 using the AIHW health price index. Differences between the DAPA-HF and Scuffham et al. (2017) populations suggested that the disease management costs may not be applicable to the DAPA-HF population. Disease management costs were applied to patients in the 'alive' health state as a static annual cost. This was unlikely to reflect the progressive nature of the disease, given that patients with worsening heart failure would be expected to have increasing care needs and hence increasing costs over time.	Moderate, favours dapagliflozin
Health state utilities	Health state utility for the 'alive' health state for the first four years of the model was based on the baseline utility value for the placebo arm of the DAPA-HF trial. In subsequent cycles, the resubmission applied an age-related decline in utility based on Australian population utility estimates reported by Hawthorne et al. (2013). The methods used to model utility values over time were not adequately justified and were considered highly uncertain. It was unclear whether the derived utility values adequately captured underlying quality of life over time in the modelled HFrEF population. Additionally, the applicability of the population utility estimates to the decline in quality of life in the HFrEF population over time was unclear. The resubmission did not adequately justify the validity of the approach and did not present studies to validate the resulting utility estimates.	Moderate, favours dapagliflozin

Source: Compiled during the evaluation with reference to Section 3B of the resubmission, and the 'Dapagliflozin HF_PBAC Mar 2021_CE Model' Excel workbook.
AIHW, Australian Institute of Health and Welfare; HFrEF, heart failure with reduced ejection fraction.
The redacted values correspond to the following ranges:
[1] *$15,000 to < $25,000*
[2] *$25,000 to < $35,000*

6.27 As described in the table above, the use of general population mortality rates and general population utility values to extrapolate the mortality and utility estimates from the DAPA-HF trial was not adequately justified in the resubmission. The resulting mortality and utility estimates used in the model may not reflect the mortality risk and utility change over time among patients with HFrEF. The PSCR argued that the economic model did not directly apply mortality rates nor utilities from the general population. Rather, it used these data to estimate age-related trends in mortality and utilities (for application to Cycle 2 and beyond). It claimed that there was no evidence that age-related proportional changes to mortality and utilities were different for the target PBS population than for the general population (the pre-PBAC response reiterated this argument). Nonetheless, the ESC noted that there was no evidence that the values would be the same, and hence agreed with the Commentary that the submission's approaches were poorly justified. The ESC also noted that the submission had not justified why trial-based utilities were not applied in the model. The pre-PBAC response presented sensitivity analyses that assumed age-related proportional changes to mortality were 50% and 100% higher than those assumed in the base case model; the ICERs were, respectively, $15,000 to < $25,000 and $15,000 to < $25,000 per QALY saved (compared to the base case of $15,000 to < $25,000).

6.28 Figure 1 presents the model trace for dapagliflozin plus standard care and placebo plus standard care.

Figure 1: Model traces for dapagliflozin plus standard care and placebo plus standard care



Source: Compiled using 'Dapagliflozin HF_PBAC Mar 2021_CE Model' Excel workbook.
CV, cardiovascular; DAP, dapagliflozin; PBO, placebo.

6.29 The model traces indicated that dapagliflozin was associated with a survival benefit, and that this was predominantly due to a reduction in cardiovascular deaths. All patients had died by 20 years in the model.

6.30 The results of the modelled economic evaluation are summarised below.

Table 9: Results of the modelled economic evaluation

Component	Dapagliflozin + SOC	Placebo + SOC	Increment
Costs	$[redacted]	$24,452	$[redacted]
Life years	5.42	4.89	0.53
QALYs	3.92	3.55	0.37
Incremental cost/QALY gained			$[redacted][1]

Source: Table 3.4-16, p176 of the resubmission.
QALY, quality-adjusted life year; SOC, standard care.
Note: results incorporate the sacubitril/valsartan published price, which is subject to a Special Pricing Arrangement.
The redacted values correspond to the following ranges:
[1] *$15,000 to < $25,000*

6.31 Based on the modelled economic evaluation, treatment with dapagliflozin plus standard care (including a beta-blocker plus an ACE inhibitor or ARB in 89.3% of patients and a beta-blocker plus an ARNI in 10.7% of patients) was associated with a cost of $15,000 to < $25,000 per QALY gained. Results based on the subgroup of patients not receiving an ARNI as background therapy, and the subgroup of patients receiving an ARNI as background therapy were $15,000 to < $25,000 and $25,000 to < $35,000 per QALY gained, respectively.

6.32 The pre-PBAC response presented a revised base-case ICER, incorporating an increased treatment initiation age, a waning treatment effect, an increase in the proportion of background ARNI use, and a reduction in the dapagliflozin price.

Table 10: Revised base case ICER

Scenario	ICER ($/QALY gained)
Resubmission base case	[redacted][3]
Revised base case:	
Increased age from 66 to 68 years[1]	[redacted][3]
Waning treatment effect from Cycle 2 to 15 years	[redacted][4]
Proportion of ARNI use increased from 10.7% to 20%[2]	[redacted][4]
Revised DPMQ ($[redacted] to [redacted] DPMQ $[redacted])	[redacted][3]

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

ARNI, angiotensin-receptor neprilysin inhibitor; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SOC, standard of care.

[1] Reported as average age of sponsor's patient familiarisation program.

[2] Based on EMPEROR-Reduced (19%) and clinical opinion; noted in paragraph 7.5, dapagliflozin, PSD, November 2020 PBAC meeting.

Note: results incorporate the sacubitril/valsartan published price, which is subject to a Special Pricing Arrangement.

The redacted values correspond to the following ranges:

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

[4] $25,000 to < $35,000

6.33 The results of key sensitivity analyses are summarised below.

Table 11: Results of sensitivity analyses (note – these are not updated with the pre-PBAC response price offer)

Analyses	Incremental cost	Incremental QALY	ICER
Base case	**$** [redacted]	**0.37**	**$** [redacted] [1]
Time horizon (base case: 30 years)			
- 1.52 years (resubmission's trial-based analysis)	$ [redacted]	0.01	$ [redacted] [2]
- 5 years[1]	$ [redacted]	0.11	$ [redacted] [3]
- 10 years	$ [redacted]	0.29	$ [redacted] [1]
- 15 years	$ [redacted]	0.36	$ [redacted] [1]
- 20 years[1]	$ [redacted]	0.37	$ [redacted] [1]
Proportion treated with an ARNI (base case: 10.7%)			
- 100%	$ [redacted]	0.19	$ [redacted] [4]
- 20%	$ [redacted]	0.35	$ [redacted] [1]
- 0%	$ [redacted]	0.39	$ [redacted] [1]
Proportion with T2DM (base case: 45.1%)			
- 100%	$ [redacted]	0.48	$ [redacted] [1]
- 22.5%	$ [redacted]	0.30	$ [redacted] [1]
- 0%	$ [redacted]	0.25	$ [redacted] [4]
Dapagliflozin discontinuation (base case: log-normal extrapolation)			
- Exponential extrapolation[1]	$ [redacted]	0.37	$ [redacted] [1]
- Weibull extrapolation[1]	$ [redacted]	0.37	$ [redacted] [1]
- Gompertz extrapolation[1]	$ [redacted]	0.37	$ [redacted] [1]
- No discontinuations	$ [redacted]	0.37	$ [redacted] [1]
'Alive' health state utility at baseline (base case: 0.74)			
- 0.77 (DAPA-HF at 12 months)	$ [redacted]	0.39	$ [redacted] [1]
- 0.65 (Adena et al., 2019; post HF hospitalisation)	$ [redacted]	0.32	$ [redacted] [1]
Disease management costs (base case: $3,256 / year)[1]			
- Doubled ($6,512 / year)	$ [redacted]	0.37	$ [redacted] [1]
- Halved ($1,628 / year)	$ [redacted]	0.37	$ [redacted] [1]
Mortality (base case: dapagliflozin and placebo independent)[1]			
- Dapagliflozin same as placebo after 2 years	$ [redacted]	0.11	$ [redacted] [5]
- Dapagliflozin same as placebo after 5 years	$ [redacted]	0.23	$ [redacted] [4]
- Dapagliflozin same as placebo after 10 years	$ [redacted]	0.34	$ [redacted] [1]
Age-related increase in HF hospitalisations (base case: excluded)			
- Included	$ [redacted]	0.37	$ [redacted] [1]
HF hospitalisations (base case: dapagliflozin, placebo independent)[1]			
- Dapagliflozin same as placebo after 2 years	$ [redacted]	0.37	$ [redacted] [1]
- Dapagliflozin same as placebo after 5 years	$ [redacted]	0.37	$ [redacted] [1]
- Dapagliflozin same as placebo after 10 years	$ [redacted]	0.37	$ [redacted] [1]
Heart failure hospitalisation costs (base case: $8,116)[1]			
- Doubled ($16,232)	$ [redacted]	0.37	$ [redacted] [1]
- Halved ($4,058)	$ [redacted]	0.37	$ [redacted] [1]

Source: Compiled using the 'Dapagliflozin HF_PBAC Mar 2021_CE Model' Excel workbook.

ARNI, angiotensin receptor neprilysin inhibitor; ICER, incremental cost-effectiveness ratio; T2DM, Type 2 diabetes mellitus.

[1] Sensitivity analyses conducted during evaluation.

Note: results incorporate the sacubitril/valsartan published price, which is subject to a Special Pricing Arrangement.

The redacted values correspond to the following ranges:

[1] $15,000 to < $25,000

[2] $115,000 to < $135,000

[3] $35,000 to < $45,000

[4] $25,000 to < $35,000

[5] $45,000 to < $55,000

6.34 The model was most sensitive to changes in the time horizon, mortality rate assumptions, the baseline health state utility, and the heart failure disease management costs.

Drug cost/patient/year

6.35 The dapagliflozin drug cost per patient per year was $[redacted] 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 the financial estimates due to differences in assumptions relating to treatment adherence and treatment persistence. The original and revised DPMQs are shown in the table below.

Table 12: Drug cost per patient per year for dapagliflozin

	DAPA-HF trial	Economic model		Financial estimates
Daily dose	10 mg daily	10 mg daily		10 mg daily
Cost per pack of 28 tablets (resubmission DPMQ)	-	$[redacted]		$[redacted]
Cost per pack of 28 tablets (pre-PBAC response price)[1]		$[redacted]		$[redacted]
Adherence	96.7%	100%		85%
Number of scripts per year	-	13.045 (=365.25/28 x 100%)		11.088 (=365.25/28 x 85%)
Cost per year (resubmission 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 18.2 months, 89.5% of patients in the dapagliflozin arm remained on treatment.	<u>No ARNI subgroup</u> Year 1: 100% Year 2: 92% Year 3: 88% Year 4: 85% Year 5: 83% Year 6: 81%	<u>ARNI subgroup</u> Year 1: 100% Year 2: 89% Year 3: 85% Year 4: 83% Year 5: 81% Year 6: 79%	100%

Source: Table 4.2-2, pp185-186 of the resubmission; Table 14.1.1, p144; Table 14.1.9, p369 of the DAPA-HF clinical study report; 'DrugSurv' worksheet of the 'Dapagliflozin HF_PBAC Mar 2021_CE Model' Excel workbook.
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

6.36 The resubmission was not considered by DUSC. Compared to the November 2020 submission, the main changes to the financial estimates were:

- The use of an epidemiological approach to estimate the financial impacts of listing dapagliflozin for HFrEF (previously a mixed epidemiological and market share approach).
- Updates to the epidemiological inputs used to derive the financial impacts, including the estimated Australian adult heart failure prevalence (increased from 1.5% to 2.199%); the proportion of patients with HFrEF (reduced from 64% to 57%); the proportion of patients receiving optimised standard care (reduced from 95% to 90%); the proportion of patients not already taking an SGLT2 inhibitor (reduced from 88.4% to 80.0%); the dapagliflozin uptake rates ([redacted]% in Year 1 to [redacted]% in Year 6; increased from 5% in Year 1 to 42% in Year 6); and the dapagliflozin compliance rate (reduced from 95% to 85%).

- Removal of PBS and MBS cost offsets associated with displaced sacubitril/valsartan prescriptions.

6.37 Key inputs used to derive the financial estimates are presented in the table below.

Table 13: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Australian prevalence of HF	Adult prevalence of 2.199% based on the SHAPE study (Liew et al., 2020; N=12,968).	Prevalence estimate increased from the November 2020 submission prevalence estimate of 1.5% (midpoint of 1.0% and 2.0% reported in a systematic review reported by Sahle et al., 2016).
Proportion of patients with HFrEF	57%; sponsor assumption.	Reduced from the November 2020 submission estimate of 64% (Adabag et al., 2012). DUSC previously noted that data from an analysis of the SHAPE study suggested that 62% of heart failure patients may be HFrEF and data from the SNAPSHOT-HF study suggested 58% of acute heart failure admissions were HFrEF (paragraph 6.60, dapagliflozin, PSD, November 2020 PBAC meeting).
Proportion of patients with NYHA Class II-IV	95%; based on the proportion of patients with Class II-IV HF used in the July 2016 sacubitril/valsartan resubmission.	Unchanged from the November 2020 submission.
Proportion of patients receiving optimised standard care	90%; sponsor assumption.	Reduced from the November 2020 submission estimate of 95% (based on the assumption that the proportion of patients not receiving standard care would be less than 100% due to inability to tolerate standard care treatments, or choice not to be treated with standard care). This proportion was considered uncertain. The proposed restriction includes treatment of patients who are contraindicated or intolerant to standard care therapies. *The PBAC view is in section 7.*
Proportion of patients not receiving an SGLT2 inhibitor for T2DM	80%; sponsor assumption.	Reduced from the November 2020 submission estimate of 88.4% (derived from a sponsor-commissioned 10% Medicare analysis of patients coadministering sacubitril/valsartan and an SGLT2 inhibitor). This proportion was considered uncertain and may be impacted by changes to dapagliflozin (and SGLT2 inhibitor) positioning in T2DM treatment guidelines. *The PBAC view is in section 7.*
Dapagliflozin uptake	Yr 1: [redacted]%; Yr 2: [redacted]%; Yr 3: [redacted]%; Yr 4: [redacted]%; Yr 5: [redacted]%; Yr 6: [redacted]%; sponsor assumption.	The November 2020 submission assumed uptake rates of Yr 1: [redacted]%; Yr 2: [redacted]%; Yr 3: [redacted]%; Yr 4: [redacted]%; Yr 5: [redacted]%; Yr 6: [redacted]%. DUSC previously noted that uptake was likely to be higher as dapagliflozin is already well-known to prescribers with a favourable safety profile relative to sacubitril/valsartan (paragraph 6.60, dapagliflozin, PSD, November 2020 PBAC meeting). The resubmission uptake rates were considered uncertain. *The PBAC view is in section 7.*
Dapagliflozin compliance	85%; sponsor assumption.	Reduced from November 2020 estimate of 95%. Compliance rates were considered uncertain. The mean compliance reported in the dapagliflozin arm of the DAPA-HF trial was 97%. *The PBAC view is in section 7.*

Source: Figure 4.1.2, p182; Table 4.2-2, pp185-186 of the resubmission.
DUSC, drug utilisation sub-committee; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; SGLT2, sodium-glucose co-transporter 2; Yr, Year.

6.38 Table 14 presents the estimated net cost to the PBS/RPBS of listing dapagliflozin for HFrEF, based on the resubmission's DPMQ of $[redacted]. This table also shows the pre-PBAC response's revised estimates based on the price of $[redacted].

Table 14: Estimated net cost to the PBS/RPBS of listing dapagliflozin for HFrEF

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Eligible patients						
Australian population ≥18 years	20,757,917	21,082,471	21,411,852	21,744,502	22,073,220	22,393,101
Heart failure prevalence (2.199%)	456,467	463,604	470,847	478,162	485,390	492,424
Patients with HFrEF (57%)	260,186	264,254	268,383	272,552	276,672	280,682
Patients with Class II-IV (95%)	247,177	251,041	254,963	258,925	262,839	266,648
Proportion receiving optimised standard care (90%)[1]	222,459	225,937	229,467	233,032	236,555	239,983
Patients not already on an SGLT2 inhibitor (80%)	177,967	180,750	183,574	186,426	189,244	191,986
Dapagliflozin uptake	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Total dapagliflozin patients	[redacted][4]	[redacted][5]	[redacted][6]	[redacted][7]	[redacted][8]	[redacted][8]
Grandfathered patients	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]
Total treated patients	[redacted][4]	[redacted][10]	[redacted][6]	[redacted][7]	[redacted][8]	[redacted][8]
Total dapagliflozin scripts (13.04 per year x 85% compliance)	[redacted][11]	[redacted][12]	[redacted][13]	[redacted][14]	[redacted][15]	[redacted][15]
Net cost to the PBS/RPBS						
PBS/RPBS cost ($107.01 per script)	$[redacted][16]	$[redacted][17]	$[redacted][18]	$[redacted][19]	$[redacted][19]	$[redacted][19]
Patient co-payment ($12.81 per script)	$[redacted][20]	$[redacted][20]	$[redacted][20]	$[redacted][21]	$[redacted][21]	$[redacted][21]
Net cost to the PBS/RPBS	$[redacted][16]	$[redacted][17]	$[redacted][22]	$[redacted][23]	$[redacted][19]	$[redacted][19]
Net cost to the PBS/RPBS ($[redacted] per script, pre-PBAC response price)[3]	$[redacted][21]	$[redacted][16]	$[redacted][24]	$[redacted][25]	$[redacted][17]	$[redacted][26]
Dapagliflozin November 2020[2]						
Net cost to PBS/RPBS	$[redacted][21]	$[redacted][24]	$[redacted][25]	$[redacted][17]	$[redacted][26]	$[redacted][18]
Net saving to MBS	$[redacted][20]	$[redacted][20]	$[redacted][20]	$[redacted][20]	$[redacted][20]	$[redacted][20]
Net cost to Government	$[redacted][21]	$[redacted][24]	$[redacted][25]	$[redacted][17]	$[redacted][26]	$[redacted][18]

Source: Figure 4.2-2, pp185-186; Table 4.2-4, p187; Table 4.2-10, p191; Table 4.2-12, p193 of the resubmission; Table 4.2, p83 of the November 2020 dapagliflozin Commentary; Table 3, p2 of the pre-PBAC response.

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; HFrEF, heart failure with reduced ejection fraction; SGLT2, sodium-glucose co-transporter 2.

[1] Comprising a beta-blocker plus an ACE inhibitor or ARB or ARNI.

[2] Based on published prices of sacubitril/valsartan. The net cost to the PBS would have been reduced once the effective price was applied.

[3] 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].

The redacted values correspond to the following ranges:

[4] 20,000 to < 30,000
[5] 40,000 to < 50,000
[6] 60,000 to < 70,000
[7] 80,000 to < 90,000
[8] 100,000 to < 200,000
[9] 500 to < 5,000
[10] 50,000 to < 60,000
[11] 200,000 to < 300,000
[12] 500,000 to < 600,000
[13] 700,000 to < 800,000
[14] 900,000 to < 1,000,000
[15] 1,000,000 to < 2,000,000
[16] $20 million to < $30 million
[17] $50 million to < $60 million
[18] $80 million to < $90 million
[19] $100 million to < $200 million
[20] $0 to < $10 million
[21] $10 million to < $20 million
[22] $70 million to < $80 million

[23] *$90 million to < $100 million*
[24] *$30 million to < $40 million*
[25] *$40 million to < $50 million*
[26] *$60 million to < $70 million*

6.39 The estimated net cost to the PBS/RPBS was $20 million to < $30 million in Year 1 of listing, increasing to $100 million to < $200 million in Year 6, an estimated net cost of $400 million to < $500 million over the first six years of listing. The November 2020 submission estimated a net cost to the PBS/RPBS of $200 million to < $300 million over the first six years of listing. The higher net cost to the PBS/RPBS was predominantly due to a higher estimated prevalence rate of heart failure, the assumption of increased uptake rates for dapagliflozin, and the removal of cost offsets associated with dapagliflozin substitution for sacubitril/valsartan.

6.40 The revised price in the pre-PBAC response (DPMQ $[redacted]) resulted in a net cost to the PBS/RPBS of $10 million to < $20 million in Year 1 of listing, increasing to $60 million to < $70 million in Year 6, an estimated net cost of $200 million to < $300 million over the first six years of listing.

6.41 The evaluation considered the utilisation/financial estimates to be highly uncertain due to the following issues:

- The assumed dapagliflozin uptake rates were uncertain. Factors that could result in higher uptake rates are the familiarity with dapagliflozin in the treatment of diabetes, the favourable results for SGLT2 inhibitors in heart failure clinical trials, and the inclusion of dapagliflozin in Australian heart failure treatment guidelines. Lower uptake of dapagliflozin may result from prescribing of alternative SGLT2 inhibitors (e.g. empagliflozin) with evidence in HFrEF for patients with T2DM.
- The proportion of patients with T2DM and HFrEF who would be receiving dapagliflozin for diabetes was uncertain and may be impacted by changes to dapagliflozin (and SGLT2 inhibitor) positioning in diabetes treatment guidelines.
- DUSC previously noted that the risk of leakage is likely to be high as dapagliflozin is already well-known to prescribers and evidence shows positive outcomes for cardiovascular disease, heart failure with reduced/preserved ejection fraction and potentially chronic kidney disease, and that there may also be an increase in patients utilising the T2DM restriction due to these positive outcomes for other diseases (paragraph 6.60, dapagliflozin, PSD, November 2020 PBAC meeting). The PBAC noted a recent industry report showing positive outcomes for empagliflozin for use in heart failure with preserved ejection fraction (EMPEROR-Preserved)[2], and that the dapagliflozin DELIVER trial (Dapagliflozin Evaluation to Improve the LIVEs

[2] https://investor.lilly.com/news-releases/news-release-details/breakthrough-results-jardiancer-empagliflozin-confirm-emperor.

of Patients With PReserved Ejection Fraction Heart Failure; NCT03619213) was expected to be completed in early 2022[3].

- The resubmission did not include any cost offsets associated with substitution of sacubitril/valsartan for dapagliflozin. The PBAC previously considered that dapagliflozin has a different mechanism of action compared to sacubitril/valsartan, and patients will potentially switch from, add-on, or displace sacubitril/valsartan, or grow the current heart failure market (paragraph 7.3, dapagliflozin, PSD, November 2020 PBAC meeting).

6.42 The PSCR advised that grandfathered patients (N=500 to < 5,000 in Year 1 in Table 14 above) were not included in the prevalent patient pool. It was assumed that all patients in the grandfathered cohort would continue taking dapagliflozin (100% uptake in all 6 years) as long as they stayed alive. Hence, the only attrition in use of dapagliflozin occurred as a result of death. The ESC noted that it was unclear if the prevalent patient population may have double-counted the grandfathered population.

Quality Use of Medicines

6.43 The resubmission presented expert opinion to address the quality use of medicines issues raised by DUSC and the PBAC in relation to the November 2020 submission. The resubmission also provided a list of current and future activities, which it stated would support the quality use of medicines in relation to dapagliflozin for the treatment of HFrEF. The resubmission claimed that quality use of medicines issues raised in relation to switching from sacubitril/valsartan were no longer relevant as the comparator nominated in the resubmission is standard of care alone. However, this was not reasonable given that some switching from sacubitril/valsartan to dapagliflozin may occur in clinical practice.

Financial Management – Risk Sharing Arrangements

6.44 As noted above, DUSC previously advised that the risk of leakage outside the proposed PBS population was high. The PSCR had claimed that the restriction wording, a proposed weighted price, and a Risk Sharing Arrangement (RSA) would address the risk of leakage. The ESC considered that the resubmission's estimates (particularly with respect to the overlapping population with T2DM) were unreliable, and that there remained a particular risk that the Australian Government would pay more for patients with T2DM who are already receiving, or eligible to receive, cardiovascular benefits at a substantially lower price. It considered that the RSA and proposed weighted price did not mitigate this risk. The pre-PBAC response presented a 'risk of leakage' assessment, and 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

[3] https://clinicaltrials.gov/ct2/show/NCT03619213.

between T2DM, HF and CKD. The PBAC noted the revised price offer did not address the risk of use in the HFpEF population.

Additional Information

6.45 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 T2DM 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 (refer to agenda item 6.03), the projected utilisation on 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 heart failure with reduced ejection fraction (HFrEF). 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] PBS price 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 risk of use outside the proposed PBS restriction. The PBAC noted that although the resubmission had presented additional information to estimate the overall net impact of listing for both HFrEF and CKD (see agenda item 6.03, 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 resubmission for HFrEF (and the submission for CKD).

7.2 The PBAC noted that the resubmission for HFrEF had addressed its *main* concerns with the November 2020 submission in terms of a revised comparator, clinical place in therapy, the type of economic analysis, the financial estimates and quality use of medicines (see Table 2 and paragraphs below for more details).

7.3 The PBAC considered that the resubmission's nominated main comparator was in line with the PBAC's previous advice (i.e. beta-blocker plus an ACE inhibitor or ARB (with or without an MRA and other heart failure medications) to be the comparator for the majority of patients (80-89%)), with the addition of an ARNI instead of an ARB in the remaining patients.

7.4 The PBAC remained of the view that the clinical place of dapagliflozin for heart failure was not yet established and was likely to continue to evolve. It reaffirmed its advice

that given that dapagliflozin has a different mechanism of action to sacubitril/valsartan, patients will potentially switch from, add-on, or displace sacubitril/valsartan, or grow the current heart failure market. The PBAC recognised that SGLT2 inhibitors are gaining increasing prominence in international clinical guidelines for heart failure, and as such it considered that the comparator mix presented in the resubmission represented the vast majority of expected use and that it was reasonable that the economic model and financial estimates did not account for patients switching between sacubitril/valsartan and dapagliflozin.

7.5 The PBAC reaffirmed its previous advice that the DAPA-HF trial supported a claim, with a high level of certainty, that dapagliflozin added to standard of care had a moderate benefit, and non-inferior safety, compared with standard of care alone.

7.6 The resubmission presented a cost utility analysis of dapagliflozin plus standard care versus standard care alone, using a two-state model structure. The PBAC agreed with the ESC that this structure was overly simplistic and did not adequately reflect the progressive nature of heart failure, and associated changes in costs, quality of life and mortality risk. 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.

7.7 The PBAC noted the revised base case presented in the pre-PBAC response was an ICER of $15,000 to < $25,000 per QALY gained, incorporating the price reduction to [redacted] the [redacted] price and various other adjustments (see Table 10). 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 an HFrEF listing would be cost effective at the [redacted] price.

7.8 In terms of the financial implications, the PBAC noted the evaluation highlighted that a number of uncertainties remained, including the proportion of patients receiving optimised standard care, the proportion of patients not already receiving an SGLT2 inhibitor for T2DM, and the dapagliflozin uptake and compliance rates (see Table 13 and paragraph 6.41). The PBAC noted the ESC's advice that the resubmission's estimates (particularly with respect to the overlapping population with T2DM) were unreliable, and the PBAC also recalled the DUSC's advice that that the risk of leakage is likely to be high (paragraph 6.60, dapagliflozin, PSD, November 2020 PBAC meeting). The PBAC then noted that the pre-PBAC response presented a 'risk of leakage' assessment, in which the sponsor was of the strong opinion that a price reduction to match the [redacted] DPMQ negated the need for an RSA, as it would alleviate the risk of leakage between T2DM, HF and CKD.

7.9 The PBAC acknowledged that the resubmission had amended the financial estimates in line with the previous DUSC advice, and it considered that the values outlined in Table 13 were reasonable assumptions based on the available sources (with respect to the overlapping population with T2DM, the PBAC reached this view specifically in

the context of the pre-PBAC price reduction). Importantly, however, the PBAC did not consider that the price reduction removed the risk of use in patients with heart failure with preserved ejection fraction, noting the emerging evidence for SGLT2 inhibitor use in this population and a lack of other available therapies. It recommended that an RSA would be needed to manage the high and increasing risk of use in this group. The PBAC also noted that grandfathered patients appeared to be double counted (the PSCR had suggested these patients were not included in the prevalent pool, but no evidence was presented to support this claim). Overall, the PBAC had moderate certainty with respect to the financial estimates for HFrEF, but 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.

7.10 The PBAC considered that the proposed restriction shown under the *Requested listing* heading above was appropriate, noting that the 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.

Outcome:
Deferred

Addendum to the July 2021 PBAC Minutes:

4.03 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 heart failure with reduced ejection fraction (HFrEF). The PBAC also deferred its decision with respect to a concurrent submission for dapagliflozin for CKD. As noted in paragraph 7.1 above, the decision was deferred as the resubmission 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 7.9).

8.2 The department obtained additional information from the sponsor in August 2021, which the PBAC considered at its September 2021 meeting.

8.3 The PBAC had previously considered that the financial estimates for HFrEF presented in the July 2021 submission were based on reasonable assumptions considering the available evidence, although it had noted uncertainties raised in the evaluation in relation to the proportion of patients receiving optimised standard care, the proportion of patients not already receiving an SGLT2 inhibitor for T2DM, and the dapagliflozin uptake and compliance rates (paragraph 7.8 and 7.9 above).

8.4 The PBAC had also previously noted there was a risk of use in heart failure with preserved ejection fraction, given the emerging evidence for SGLT2 inhibitor use in this population and a lack of other available therapies. The PBAC recommended that an RSA was needed to manage the high and increasing risk of use outside of HFrEF (paragraph 7.9).

9 Consideration of the evidence

Revised HFrEF estimates

9.1 Compared to the July 2021 submission, the overall financial estimates presented by the sponsor were reduced ($200 million to < $300 million versus $200 million to < $300 million over six years, see Table 16 below). This was mainly due to the removal of grandfathered patients from forecasts of the number of eligible prevalent patients. The sponsor also increased the Year 1 treatment uptake

assumption from [redacted]% to [redacted]% claiming that this was required to account for grandfathered patients. Other aspects of the previous financial estimates modelling were unchanged and the sponsor presented further data to validate its assumption regarding the proportion of patients already treated for T2DM with a SGLT2 inhibitor (see Table 15 below).

9.2 Table 15 below outlines the methods and assumptions used in the financial estimates presented to PBAC in July 2021 and September 2021.

Table 15: Key inputs used in the financial estimates presented to PBAC in July 2021 and September 2021, for heart failure with reduced ejection fraction

Parameter	Value applied and source	
	July 2021 resubmission	**September 2021 estimates**
Australian prevalence of HF	Adult prevalence of 2.199% based on the SHAPE study (Liew et al., 2020; N=12,968). In response to DUSC advice on the November 2020 submission, the prevalence estimate increased from the November 2020 submission prevalence estimate of 1.5% (midpoint of 1.0% and 2.0% reported in a systematic review reported by Sahle et al., 2016).	Unchanged
Proportion of patients with HFrEF	57%; sponsor assumption. Reduced from the November 2020 submission estimate of 64% (Adabag et al., 2012). DUSC previously noted that data from an analysis of the SHAPE study suggested that 62% of heart failure patients may be HFrEF and data from the SNAPSHOT-HF study suggested 58% of acute heart failure admissions were HFrEF (paragraph 6.60, dapagliflozin, PSD, November 2020 PBAC meeting).	Unchanged
Proportion of patients with NYHA Class II-IV	95%; based on the proportion of patients with Class II-IV HF used in the July 2016 sacubitril/valsartan resubmission.	Unchanged
Proportion of patients receiving optimised standard care	90%; sponsor assumption. Reduced from the November 2020 submission estimate of 95% (based on the assumption that the proportion of patients not receiving standard care would be less than 100% due to inability to tolerate standard care treatments, or choice not to be treated with standard care). This proportion was considered uncertain. The proposed restriction includes treatment of patients who are contraindicated or intolerant to standard care therapies.	Unchanged. Optimised care is assumed to comprise of a beta-blocker plus an ACE-I or ARB or ARNI.

Parameter	Value applied and source	
	July 2021 resubmission	**September 2021 estimates**
Proportion of patients not receiving an SGLT2 inhibitor for T2DM	80%; sponsor assumption. Reduced from the November 2020 submission estimate of 88.4% (derived from a sponsor-commissioned 10% Medicare analysis of patients co-administering sacubitril/valsartan and an SGLT2 inhibitor). This proportion was considered uncertain and may be impacted by changes to dapagliflozin (and SGLT2 inhibitor) positioning in T2DM treatment guidelines.	Unchanged. Table 9 of the additional information presented data, which the sponsor considered validated the 80% assumption: • Advice from two heart failure specialists that around 20% of their HFrEF patients are already on an SGLT2-I for T2DM. • Analysis of a 10% PBS sample indicating between 7.1%-13.4% of patients with HFrEF will be receiving an SGLT2 inhibitor for T2DM (analysis methodology was provided in Attachment 4 Workbook sheet titled 'Eligible T2DM overlap').
Dapagliflozin uptake	Yr 1: [redacted]%; Yr 2: [redacted]%; Yr 3: [redacted]%; Yr 4: [redacted]%; Yr 5: [redacted]%; Yr 6: [redacted]%; sponsor assumption. The November 2020 submission assumed uptake rates of Yr 1: [redacted]%; Yr 2: [redacted]%; Yr 3: [redacted]%; Yr 4: [redacted]%; Yr 5: [redacted]%; Yr 6: [redacted]%. DUSC previously noted that uptake was likely to be higher as dapagliflozin is already well-known to prescribers with a favourable safety profile relative to sacubitril/valsartan (paragraph 6.60, dapagliflozin, PSD, November 2020 PBAC meeting).	Adjusted first year uptake rate from [redacted]% to [redacted]%, which the sponsor stated was to account for grandfathered patients as part of the prevalent patient population. The treatment uptake rates for subsequent years were unchanged.
Dapagliflozin compliance	85%; sponsor assumption. Reduced from November 2020 estimate of 95%. Compliance rates were considered uncertain. The mean compliance reported in the dapagliflozin arm of the DAPA-HF trial was 97%.	Unchanged
Grandfathered patients	Year 1: [redacted][1] to Year 6: [redacted][1]. ESC noted that it was unclear if the prevalent patient population may have double-counted the grandfathered population (paragraph 6.42, dapagliflozin, PSD, July 2021 PBAC meeting).	The sponsor removed separate modelling of grandfathered patients (Attachment 4, sheet '2c. Patients – GF', row 68 where uptake for grandfathered patients was set to zero). The sponsor increased the uptake rate in the first year of listing from [redacted]% to [redacted]% claiming that this was required to account for these grandfathered patients in the first year.

Source: Table 13, dapagliflozin, PSD, July 2021 PBAC meeting, Table 9, p22 of the additional information provided in August 2021; Attachment 4 financial estimates model provided with the additional information in August 2021.

The redacted values correspond to the following ranges

[1] 500 to < 5,000

9.3 The table below presents a comparison of the financial estimates between the July 2021 resubmission and the additional information considered in September 2021.

Table 16: 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	[redacted][1]	[redacted][2]	[redacted][3]	[redacted][4]	[redacted][5]	[redacted][5]	
September 2021	[redacted][1]	[redacted][6]	[redacted][3]	[redacted][4]	[redacted][5]	[redacted][5]	
Difference	-[redacted][7]	-[redacted][8]	-[redacted][8]	-[redacted][8]	-[redacted][8]	-[redacted][8]	
Scripts dispensed (13.04 scripts per year x 85% compliance for both July and September estimates)							
July 2021	[redacted][9]	[redacted][10]	[redacted][11]	[redacted][12]	[redacted][13]	[redacted][13]	
September 2021	[redacted][9]	[redacted][10]	[redacted][11]	[redacted][12]	[redacted][13]	[redacted][13]	
Difference	-[redacted][7]	-[redacted][14]	-[redacted][14]	-[redacted][14]	-[redacted][1]	-[redacted][1]	
Net cost to R/PBS (less copayments)							
July 2021 [a]	$[redacted][15]	$[redacted][16]	$[redacted] 17	$[redacted][18]	$[redacted] 19	$[redacted][20]	$[redacted][21]
September 2021 [b]	$[redacted][1] 5	$[redacted][16]	$[redacted][17]	$[redacted] 18	$[redacted][1] 9	$[redacted] 20	$[redacted][21]
Difference	-$[redacted][22]	-$[redacted][22]	-$[redacted][22]	-$[redacted][22]	-$[redacted][22]	-$[redacted][22]	-$[redacted][22]

Source: Table 18, dapagliflozin, PSD, July 2021 PBAC meeting; Table 10, p23 of the additional information provided in August 2021.

[a] Based on pre-PBAC response proposed DPMQ of $[redacted].

[b] Based on revised DPMQ $[redacted], price for the [redacted] listing as at 1 July 2021.

The redacted values correspond to the following ranges

[1]20,000 to < 30,000
[2]50,000 to < 60,000
[3]60,000 to < 70,000
[4]80,000 to < 90,000
[5]100,000 to < 200,000
[6]40,000 to < 50,000
[7]< 500
[8]500 to < 5,000
[9]200,000 to < 300,000
[10]500,000 to < 600,000
[11]700,000 to < 800,000
[12]900,000 to < 1,000,000
[13]1,000,000 to < 2,000,000
[14]30,000 to < 40,000
[15]$10 million to < $20 million
[16]$20 million to < $30 million
[17]$30 million to < $40 million
[18]$40 million to < $50 million
[19]$50 million to < $60 million
[20]$60 million to < $70 million
[21]$200 million to < $300 million
[22]$0 to < $10 million

Combined estimates for HFrEF, CKD and T2DM

9.4 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 17: 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][5]
HFrEF	NA	$[redacted][6]	$[redacted][7]	$[redacted][1]	$[redacted][8]	$[redacted][2]	$[redacted][9]
T2DM	$[redacted][8]/ $[redacted][8]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][10]	$[redacted][1] 0
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][5]	$[redacted][10]	$[redacted][10]	$[redacted][11]	$[redacted][11]	$[redacted][11]	$[redacted][12]
CKD +HFrEF +T2DM	NA	$[redacted][1] 0	$[redacted][11]	$[redacted][1] 2	$[redacted] 12	$[redacted][13]	$[redacted][1] 4

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

Proposed Risk Sharing Arrangement

9.5 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.

9.6 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 17.

9.7 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."

Clinical guidelines and requested listing

9.8 The European Society of Cardiology released its updated *Guidelines for the diagnosis and treatment of acute and chronic heart failure* on 27 August 2021[4]. The revised guidelines note (pp21-22):

- "The triad of an ACE-I/ARNI, a beta-blocker, and an MRA is recommended as cornerstone therapies for these patients, unless the drugs are contraindicated or not tolerated. They should be uptitrated to the doses used in the clinical trials (or to maximally tolerated doses if that is not possible)."
- "Unless contraindicated or not tolerated, dapagliflozin or empagliflozin are recommended for all patients with HFrEF already treated with an ACE-I/ARNI, a beta-blocker, and an MRA, regardless of whether they have diabetes or not."
- That the recommendations for use of an ACE-I, beta-blocker, MRA, and SGLTi are all Class I recommendations, based on Level A evidence.

9.9 On 1 June 2021, the beta-blocker criterion on the sacubitril + valsartan PBS listing (which was also included in the proposed dapagliflozin for HFrEF listing) was changed from:

- "Patient must receive concomitant optimal standard chronic heart failure treatment, which must include the maximum tolerated dose of a beta-blocker, unless contraindicated or not tolerated."

To:

- "Patient must receive concomitant optimal standard chronic heart failure treatment, which must include a beta-blocker, unless at least one of the following is present in relation to the beta-blocker: (i) a contraindication listed in the Product Information, (ii) an existing/expected intolerance, (iii) local treatment guidelines recommend initiation of this drug product prior to a beta-blocker."

9.10 This change to the sacubitril + valsartan PBS listing was in response to a recommendation made in November 2020 when PBAC considered that the previous criterion was "inconsistent with clinical guidelines and may complicate management of patients" (paragraph 7.6, sacubitril + valsartan, PSD, November 2020).

10 PBAC Outcome

10.1 The PBAC recommended extending the existing listing of dapagliflozin to include a General Schedule Authority Required (Streamlined) listing for the treatment of

[4] https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Acute-and-Chronic-Heart-Failure

patients with heart failure with reduced ejection fraction (HFrEF). 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] PBS price for dapagliflozin for [redacted]).

10.2 The PBAC recalled that the July 2021 resubmission had addressed its *main* concerns with respect to the comparator, clinical place in therapy, economic analysis, financial estimates and quality use of medicines (see section 7 above, notwithstanding the lack of robust economic modelling).

10.3 In terms of the financial estimates presented, the PBAC reiterated that there was a high and increasing risk of use in patients with heart failure with preserved ejection fraction. The PBAC considered that the revised estimates presented with respect to the HFrEF indication remained broadly reasonable based on the available sources of evidence. However, the PBAC noted that the sponsor had increased uptake in Year 1 from [redacted]% to [redacted]%, which it claimed was to account for the grandfathered patients (effectively, 500 to < 5,000 patients in total). The PBAC considered that these patients would have been accounted for in the prevalent pool of patients, and so additional uptake had not been justified, and should not be included in the revised estimates.

10.4 The PBAC also noted the revised estimates with respect to the CKD and T2DM populations and considered that substantial uncertainties remained (further discussed in the PSD for item 4.02 dapagliflozin for CKD, September 2021 PBAC meeting). Therefore, the PBAC considered that the estimates for HFrEF alone formed a reliable basis for a Risk Sharing Arrangement for this indication only, with a [redacted]% rebate above the expenditure caps.

10.5 Additionally, the PBAC noted that the European Society of Cardiology had recently updated its' *Guidelines for the diagnosis and treatment of acute and chronic heart failure,* and recalled recent PBS restriction changes with respect to titration and timing of beta-blocker use for patients taking sacubitril + valsartan. For the dapagliflozin listing for HFrEF, the PBAC considered that it would be similarly appropriate to be silent on titration requirements for concomitant beta-blocker/ACE-I/ARNI/ARB use, as this would be more in line with current clinical guidelines and expected practice.

10.6 The PBAC advised that dapagliflozin for HFrEF is suitable for prescribing by nurse practitioners for continuing therapy only.

10.7 The PBAC recommended that the Early Supply Rule should apply.

10.8 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for dapagliflozin:

a) The treatment is expected to provide a moderate and clinically relevant improvement in efficacy over alternative therapies, however the criteria of

providing a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over an alternative therapy was not met;

b) The treatment is expected to address a moderate unmet clinical need, rather than a high and urgent unmet need, as multiple other therapies are currently available on the PBS for this indication;

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

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

Outcome:
Recommended

11 Recommended listing

11.1 Amend existing listing:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
DAPAGLIFLOZIN					
dapagliflozin 10 mg tablet, 28	NEW	1	28	5	Forxiga
Restriction Summary [new] / Treatment of Concept: [new]					
	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: ☒ Medical Practitioners ☒ Nurse practitioners				
	Restriction type: ☒ Authority Required (STREAMLINED) [new code]				
	Indication: Chronic heart failure				
	Treatment Phase: [blank]				
	Clinical criteria:				
	Patient must be symptomatic with NYHA classes II, III or IV,				
	AND				
	Clinical criteria:				
	Patient must have a documented left ventricular ejection fraction (LVEF) of less than or equal to 40%,				
	AND				
	Clinical criteria:				
	Patient must receive concomitant optimal standard chronic heart failure treatment, which must include a beta-blocker, unless contraindicated or not tolerated;				
	AND				
	Clinical criteria:				
	Patient must be receiving treatment with an ACE inhibitor, unless contraindicated according to the TGA-approved Product Information or cannot be tolerated; or				
	Patient must be receiving treatment with an angiotensin II antagonist, unless contraindicated according to the TGA-approved Product Information or cannot be tolerated; or				
	Patient must be receiving treatment with an angiotensin receptor with neprilysin inhibitor combination therapy unless contraindicated according to the TGA-approved Product Information or cannot be tolerated,				
	AND				
	Clinical criteria:				
	Patient must not be receiving treatment with another sodium-glucose co-transporter 2 (SGLT2) inhibitor.				
	Administrative Advice: Continuing Therapy Only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.				
	Administrative advice: No increase in the maximum quantity or number of units may be authorised.				
	Administrative advice: No increase in the maximum number of repeats may be authorised.				

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

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.