An addendum to this Public Summary Document (PSD) has been included at the end of the document

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

## 1 Purpose of submission

1.1 The Category 2 submission requested a General Schedule Authority Required (Streamlined) listing for empagliflozin for the treatment of chronic heart failure (NYHA classes II, III, or IV) in patients with a left ventricular ejection fraction greater than 40%.

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

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

| Component | Description |
|---|---|
| Population | Adult patients with chronic heart failure (NYHA Class II-IV) and LVEF >40% |
| Intervention | Empagliflozin 10 mg once daily in addition to standard care |
| Comparator | Placebo, used in conjunction with standard care including diuretics for symptom relief and other concomitant medications to manage related comorbidities. |
| Outcomes | Composite of cardiovascular death and hospitalisation for heart failure, all-cause mortality, renal function decline, heart failure related quality of life, adverse events |
| Clinical claim | Empagliflozin (add-on to standard care) is superior in terms of efficacy and non-inferior in terms of safety compared to placebo (add-on to standard care). |

Source: Table 1.1, p2 of the submission.
Abbreviations: HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association

## 2 Background

### *Registration status*

2.1 **TGA status at time of PBAC consideration**: The submission was lodged under the TGA/PBAC parallel process. At the time of evaluation, the TGA Clinical Evaluator's Round 1 Report (30 April 2022) and Round 2 report (31 July 2022) were available. The Delegates Overview (6 September 2022) was received prior to the ESC meeting. The Minutes of the TGA Advisory Committee on Medicines (ACM) were received prior to the PBAC meeting. The ACM considered empagliflozin to have an overall positive benefit-risk profile for use in adult patients for the treatment of symptomatic heart failure independent of left ventricular ejection fraction, as an adjunct to standard of care therapy.

2.2 The proposed extension of the TGA indication for empagliflozin 10 mg tablets was:

*Adults for the treatment of symptomatic heart failure independent of left ventricular ejection fraction, as an adjunct to standard of care therapy.*

2.3 Empagliflozin 25 mg and 10 mg tablets are listed on the Australian Register of Therapeutic Goods (ARTG) for type 2 diabetes as monotherapy, add-on combination therapies with other diabetes medicines including insulin, when diet and exercise alone do not provide adequate glycaemic control; to reduce the risk of cardiovascular death in patients with type 2 diabetes and established cardiovascular disease in conjunction with other measures to reduce cardiovascular risk in line with the current standard of care; and for the treatment of symptomatic heart failure (NYHA class II-IV) with reduced ejection fraction, as an adjunct to standard of care therapy (10 mg dose only).

2.4 Empagliflozin was FDA approved for reducing the risk of cardiovascular death and hospitalisation for heart failure in adults with heart failure in February 2022; and was approved by the EMA for treatment of adults with symptomatic chronic heart failure in March 2022. Both FDA and EMA indications are for adults with heart failure independent of LVEF level.

### *Previous PBAC consideration*

2.5 Empagliflozin has existing PBS listings for the treatment of type 2 diabetes. In addition, empagliflozin was listed on the PBS for the treatment of patients with chronic heart failure with reduced ejection fraction (LVEF ≤40%) on 1 April 2022, following a submission to the PBAC in November 2021. The PBAC has not previously considered empagliflozin or any other sodium glucose co transporter 2 (SGLT2) inhibitor for patients with chronic heart failure and LVEF>40%.

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

## 3 Requested listing

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

| **MEDICINAL PRODUCT medicinal product pack** | **Dispensed Price for Max. Qty** | **Max. qty packs** | **Max. qty units** | **№.of Rpts** | **Available brands** |
|---|---|---|---|---|---|
| EMPAGLIFLOZIN | | | | | |
| empagliflozin 10 mg tablet, 30 | $60.16 | 1 | 30 | 5 | Jardiance |
| | | | | | |
| **Restriction Summary / Treatment of Concept:** | | | | | |
| **Category / Program:** GENERAL – General Schedule (Code GE) | | | | | |
| **Prescriber type:** ☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives | | | | | |
| **Restriction type:** ☒Authority Required (Streamlined) | | | | | |
| **Administrative Advice:**<br>**Continuing Therapy Only:**<br>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.* | | | | | |
| **Indication:** Chronic heart failure | | | | | |
| **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 greater than 40% | | | | | |
| **AND** | | | | | |
| **Clinical criteria:** | | | | | |
| ~~Patient must have documented evidence of *at least one of:*~~<br>~~*(i) relevant* structural changes in the heart on echocardiography; OR~~<br>~~(ii) diastolic dysfunction with high filling pressure on echocardiography; OR~~<br>~~(iii) hospitalisation *due to* heart failure; OR~~<br>~~(iv) elevated N-terminal pro brain natriuretic peptide (NT-proBNP) level s~~<br><br>*Patient must have documented evidence of:*<br>*Structural changes in the heart on echocardiography that would be expected to cause diastolic dysfunction (e.g. left ventricular hypertrophy); AND*<br>*At least one of*<br>*(i) diastolic dysfunction with high filling pressure on echocardiography, stress echocardiography or cardiac catheterisation; OR*<br>*(ii) hospitalisation for heart failure in the 12 months prior to initiating treatment with this drug OR*<br>*(iii) requirement for intravenous diuretic therapy in the 12 months prior to initiating treatment with this drug OR*<br>*(iv) elevated N-terminal pro brain natriuretic peptide (NT-proBNP) levels in the absence of another cause* | | | | | |
| **AND** | | | | | |
| **Clinical criteria:** | | | | | |
| Patient must not be receiving treatment with another sodium-glucose co-transporter 2 (SGLT2) inhibitor. | | | | | |

Note: The submission requested a DPMQ of $60.10 from an AEMP of $44.66 using mark-ups at 1 June 2022. Based on mark-ups from 1 July 2022, the DPMQ is $60.16.

3.2 The requested dispensed price for empagliflozin of $60.16 (updated to current fees and markups) is the same as the PBS listed price of empagliflozin 10 mg tablets for type 2 diabetes and heart failure with LVEF ≤40%.

3.3 The requested restriction did not include the 25 mg empagliflozin dose strength as investigation of the cardiovascular safety of empagliflozin in type 2 diabetes found no additional cardiovascular benefits compared to the 10 mg dose (EMPA-REG OUTCOME trial).

3.4 The requested PBS restriction was broadly aligned with the inclusion criteria of the key clinical trial (EMPEROR-Preserved):

- 'Patients must be symptomatic with NYHA classes II, III or IV' (in EMPEROR-Preserved, patients at baseline were class I: 0.1%, class II: 81.5%, class III: 18.1% and class IV: 0.3%).
- 'Patient must have a documented left ventricular ejection fraction (LVEF) of greater than 40%' (in EMPEROR-Preserved, the mean at baseline was 54.3%, evenly distributed: <50% = 33.1%; 50 to <60% = 34.4%; ≥60% = 32.5%).

3.5 The ESC noted that the clinical criteria proposed by the submission were based on the clinical trial, however considered these were somewhat open to interpretation due to the nature of the criteria. The requested restriction for patients with LVEF >40% is similar to the current empagliflozin and dapagliflozin restrictions for patients with LVEF ≤40%, with both restrictions specifying patients with chronic heart failure, with NYHA classes II, III or IV, and a specification of relevant LVEF thresholds for each patient group. However, the requested restriction for LVEF >40% did not include a requirement for concomitant optimal standard chronic heart failure treatment including a beta-blocker and an ACEi/ARB/ARNi (which currently applies in the restriction for patients with LVEF ≤40%). The ESC considered this was appropriate, as there is a lack of evidence for specific disease-modifying therapies for heart failure patients with preserved ejection fraction.

3.6 In addition, the requested restriction specifies requirements for additional diagnostic testing to assess eligibility for treatment with empagliflozin. Heart failure guidelines recommend this additional diagnostic testing to confirm a diagnosis of heart failure with preserved ejection fraction. However, one of the proposed diagnostic tests (NT-proBNP testing) is not routinely used in Australian clinical practice (Chew 2021). The Pre-Sub-Committee Response (PSCR) stated that a new or modified MBS item for NT-proBNP is not required for the listing of empagliflozin in HF patients with LVEF >40% because a) only a minor subset of HF patients with LVEF >40% would access reimbursed empagliflozin treatment via the NT-proBNP criterion alone; b) the importance of NT-proBNP as a diagnostic tool for HF in the rare instances where other diagnostic outcomes are not available or where diagnosis is uncertain; and c) the treatment effect of empagliflozin is independent of baseline NT-proBNP levels. The ESC proposed that the criterion in relation to NT-proBNP testing should be retained as one of the options for determination of eligibility for empagliflozin, however it should only apply for patients with elevated NT-proBNP levels "in the absence of another cause" (e.g. pulmonary embolism).

3.7 The ESC recommended a revision to the restriction to reflect that the requirement for documented evidence of structural changes in the heart on echocardiography would apply for all patients, in addition to at least one of four additional criteria, as shown in the restriction above.

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

# 4 Population and disease

4.1 Heart failure is a complex clinical syndrome caused by underlying structural and/or functional impairment of cardiac ventricular filling and ejection, and is characterised by symptoms of dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, reduced end-organ perfusion, venous congestion (elevated jugular venous pressure, hepatic enlargement, peripheral oedema, pulmonary oedema, pleural effusion, ascites), and fatigue. The symptoms of heart failure are most evident on exertion, but increasingly occur at rest with disease progression. Common causes of heart failure include ischaemic heart disease, valvular heart disease, cardiomyopathies, hypertension, arrhythmias, and diabetes. Chronic heart failure refers to patients with the clinical symptoms of heart failure for at least three months.

4.2 Heart failure is classified by the severity of functional symptoms and impact on daily activity; i.e. New York Heart Association (NYHA) classification, as well as left ventricular ejection fraction (National Heart Foundation of Australia).

4.3 In this document, nomenclature from the most recent American Heart Association/American College of Cardiology (AHA/ACC, Heidenreich 2022) and European Society of Cardiology (ESC 2021) heart failure guidelines are used to refer to the patient population. Patients with left ventricular ejection fraction (LVEF) ≥50% and structural and/or functional cardiac abnormalities consistent with the presence of left ventricular diastolic dysfunction and/or raised natriuretic peptides, without major reductions in systolic function, have heart failure with preserved ejection fraction (HFpEF). Those with LVEF between 41%-49% have heart failure with mildly reduced ejection fraction (HFmrEF). Patients with LVEF ≤40% have heart failure with reduced ejection fraction (HFrEF). Australian guidelines (Atherton 2018) do not recommend a 'mildly reduced' category, but group patients with LVEF between 41-49% with the HFrEF population.

4.4 Liew (2020) estimated that in 2017 there were approximately 420,000 Australian adults with heart failure (2.20% age-standardised prevalence), and 66,418 new diagnoses (0.348% age-standardised incidence). The prevalence of heart failure in Indigenous Australians is estimated to be 1.7 times that of non-Indigenous Australians (Woods 2012). Australian epidemiological studies have shown that approximately 52-59% of the heart failure patient population have HFpEF or HFmrEF (Newton 2020; Sindone 2021; Wang 2018).

4.5 A systematic review of non-interventional studies reporting survival rates for patients with chronic or stable heart failure (Jones 2019) found no significant difference in survival rates between HFrEF and HFpEF in a pooled analysis, although individual studies reported improved survival rates and lower rates of hospital admission and cardiovascular mortality for patients with HFpEF. In all the included studies reporting cause of death data by LVEF level, the proportion of total mortality attributed to cardiovascular disease and heart failure was greater for patients with HFrEF than HFpEF. The review noted that patients with HFpEF are more likely to be older and have significant comorbid disease, meaning unadjusted HFrEF and HFpEF survival rates are similar (Jones 2019). The PBAC noted that results from the placebo groups of EMPEROR-Reduced and EMPEROR-Preserved trials indicated differences in baseline risks between the two populations, and differences in absolute risk reduction in the primary composite endpoint of time to CV death or HHF, as had previously been described by ESC (see paragraph 6.11). The baseline risk for the primary composite outcome was higher in the EMPEROR-Reduced population (24.7% over a median duration of follow-up of 16 months; Table 4, empagliflozin, Public Summary Document (PSD), November 2021 PBAC meeting) compared with the EMPEROR-Preserved population (17.1%, over a median duration of follow-up of 26 months; Table 4).

4.6 Empagliflozin is a selective sodium-glucose co-transporter-2 (SGLT2) inhibitor used for the treatment of adults with type 2 diabetes. The submission acknowledged that the precise mechanism of action underlying the protective cardiovascular effects of empagliflozin in the treatment of heart failure is not understood, but noted that SGLT2 inhibitors may have renal, vascular/haemodynamic, direct cardiac, and/or metabolic effects, and that these actions are independent of the glycaemic effects of SGLT2 inhibitors.

4.7 The recommended dosing of empagliflozin for the treatment of HFmrEF/HFpEF is a 10 mg tablet orally, once daily, adjunctive to standard care.

4.8 The proposed clinical management algorithm positioned empagliflozin as an add-on to standard care in the treatment of chronic HFmrEF/HFpEF. This is broadly consistent with the requested restriction, the proposed TGA indication and the inclusion criteria of the key clinical trial. However, the proposed algorithm does not include a description of the additional diagnostic criteria for patients with HFmrEF/HFpEF specified in the proposed restriction and in Australian heart failure guidelines (Atherton 2018).

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

# 5 Comparator

5.1 The submission nominated standard care as the main comparator. The main arguments provided in support of this nomination were that there are currently no effective treatments for patients with HFmrEF/HFpEF. Rather, clinicians may choose

to use any combination of background medications specific to each patient. These may include diuretics for symptom relief, and a beta-blocker, angiotensin-converting enzyme inhibitor (ACEi), angiotensin II receptor blocker (ARB) and/or mineralocorticoid receptor antagonist (MRA) to manage comorbidities. The nominated comparator was consistent with the background medications used in the key clinical trial (EMPEROR-Preserved), and with Australian heart failure guidelines (Atherton 2018). The ESC considered that standard care was the appropriate main comparator.

5.2 Dapagliflozin may be a near-market comparator. During the evaluation, it was noted that top-line results of the DELIVER trial, a placebo-controlled RCT of dapagliflozin in addition to standard care in patients with heart failure with LVEF >40%, with or without diabetes were recently released. In the trial, dapagliflozin achieved a statistically significant reduction in the primary composite endpoint of time to first cardiovascular death or worsening heart failure event (heart failure hospitalisation or urgent heart failure visit) (AstraZeneca press release, 5 May 2022). The ESC noted that full results of the DELIVER trial were recently published (Solomon et al. 2022[1]), and the results appear to be consistent with the EMPEROR-Preserved results, noting no formal assessment of non-inferiority has been conducted.

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

# 6 Consideration of the evidence

## *Sponsor hearing*

6.1 The sponsor provided a hearing for this item. The clinician described an urgent unmet need for effective treatments for patients with HFpEF, noting that the population is growing rapidly and associated with high resource use and prolonged hospitalisations. The clinician discussed that HFpEF is associated with morbidity and mortality equal to HFrEF, and that treatment with empagliflozin is associated with meaningful benefits within 4 weeks of commencing treatment, based on the primary composite outcome in EMPEROR-Preserved (time to first cardiovascular death or hospitalisation for heart failure). The clinician described the Kansas City Cardiomyopathy Questionnaire (KCCQ) as the "gold standard" for heart failure and predictor of cardiovascular disease. The PBAC considered that the hearing was informative as it provided an expert clinical perspective on treating HFpEF. However, it was noted the clinical evidence for empagliflozin treatment in HFmrEF/HFpEF did not support equivalent risk of events or

[1] Solomon SD et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med. 2022 Sep 22;387(12):1089-1098. doi: 10.1056/NEJMoa2206286. Epub 2022 Aug 27.

absolute benefits as was evident in HFrEF as discussed in paragraph 4.5.

## *Consumer comments*

6.2 The PBAC noted and welcomed the input from one organisation via the Consumer Comments facility on the PBS website. The PBAC noted the advice received from Diabetes Australia was general in nature and supported the listing of empagliflozin, especially highlighting its benefits in the diabetic population (which was not part of the proposed listing).

## *Clinical trials*

6.3 The submission was based on one head-to-head randomised trial comparing empagliflozin plus standard care versus placebo plus standard care (EMPEROR-Preserved).

6.4 Details of the trial presented in the submission are provided in Table 2.

**Table 2: Trial and associated reports presented in the submission**

| Trial ID | Protocol title/ Publication title | Publication citation |
|---|---|---|
| EMPEROR-Preserved (Trial 1245.110) | A phase III randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic Heart Failure with preserved Ejection Fraction (HFpEF). | Clinical Trial Report, 4 August 2021 |
| | Anker SD, et al. Empagliflozin in heart failure with a preserved ejection fraction. | *New Engl J Med* 2021; 385(16):1451-61. |
| | Jamal W, et al. Evaluation of the effects of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality in patients with chronic heart failure and a preserved ejection fraction: rationale for and design of the EMPEROR-Preserved Trial. | *Eur J Heart Failure* 2019; 21(10):1279-87. |
| | Anker SD, et al. Baseline characteristics of patients with heart failure with preserved ejection fraction in the EMPEROR-Preserved trial. | *Eur J Heart Failure* 2020; 22(12):2383-92. |
| | Butler J, et al. Empagliflozin, Health Status, and Quality of Life in Patients with Heart Failure and Preserved Ejection Fraction: The EMPEROR-Preserved Trial. | *Circulation* 2021; 145(3):184-193. |
| | Butler J, et al. Early benefit with empagliflozin in heart failure with preserved ejection fraction: insights from the EMPEROR-Preserved trial. | *Eur J Heart Failure* 2022; 24(2):245-248. |

Source: Table 2.1, p46 of the submission.
Note: Abstract-only publications were excluded from this list if full-text trial publications available.

6.5 The key features of the randomised trial are summarised in Table 3.

**Table 3: Key features of the included evidence**

| Trial | N | Design/ duration | Risk of bias | Patient population | Outcomes | Use in model |
|---|---|---|---|---|---|---|
| **Empagliflozin plus standard care versus placebo plus standard care** | | | | | | |
| EMPEROR-Preserved | 5,998 | Phase III, MC, R, DB, PC;<br><br>Median duration of follow-up 26 months | Low | • Age ≥18 years<br>• Chronic HFmrEF/HFpEF with LVEF >40%<br>• Evidence of structural HF or HHF within prior 12 months<br>• NYHA Class II-IV<br>• Elevated NT-proBNP[a]<br>• eGFR ≥20 mL/min/1.73 $m^2$<br>• Standard care at investigator discretion, consistent with local and international guidelines | • Composite of time to CV death or hospitalisation for HF<br>• Time to hospitalisation for HF<br>• Time to cardiovascular death<br>• Total hospitalisations for HF<br>• Change in slope of eGFR<br>• Time to death from any cause<br>• Change in KCCQ-CSS | KCCQ-CSS scores, all-cause mortality, CV mortality, HF hospitalisation, treatment discontinuation, EQ-5D scores, adverse events |

Source: Table 2.11, pp70-71; Table 2.12, p72 of the submission; Section 2.3 and 2.4 of the submission.
Abbreviations: DB, double blind; eGFR, estimated glomerular filtration rate; HF, heart failure; HHF, hospitalisation for heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved 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; PC, placebo-controlled; R, randomised.
[a] NT-proBNP ≥300 pg/mL for patients without atrial fibrillation at screening; or ≥900 pg/mL for patients without atrial fibrillation.

6.6 The risk of bias was low in the EMPEROR-Preserved trial. Baseline patient characteristics were generally well matched between treatment arms of the EMPEROR-Preserved trial. Randomisation was stratified by region, diabetes history, LVEF and eGFR at screening. Slightly more than half the patients were males (55.3%). The majority of patients were Caucasian (75.9%) and aged 70 years or older (64.1%, mean age 71.9 years).

6.7 The submission noted that while there are no proven treatments for HFmrEF or HFpEF, most patients in the trial were being treated with standard cardiovascular drugs such as ACEi, ARBs, ARNIs at baseline (81% in empagliflozin arm and 80.4% in the placebo arm) or beta-blockers (86.7% empagliflozin arm, 85.9% placebo arm).

6.8 The submission reported Australian patient and disease characteristics from four studies of heart failure patients including those with HFmrEF/HFpEF (or HFpEF only where HFmrEF was not considered separately). Patients in the EMPEROR-Preserved trial were younger than Australian patients (mean age 71.9 years versus approximately 80 years), and there were fewer females than in the Australian patient population (44.7% female patients in the EMPEROR-Preserved trial, and between 47% to 59% in the Australian studies). There were limited data to compare NYHA class distribution in the Australian population to the trial population, with the only Australian data based on patients hospitalised with acute heart failure. The submission noted that patients in the EMPEROR-Preserved trial had a high prevalence of comorbidities such as atrial fibrillation (51.1%) and hypertension (90.6%), as expected in patients with HFpEF. The Australian studies had similar proportions of

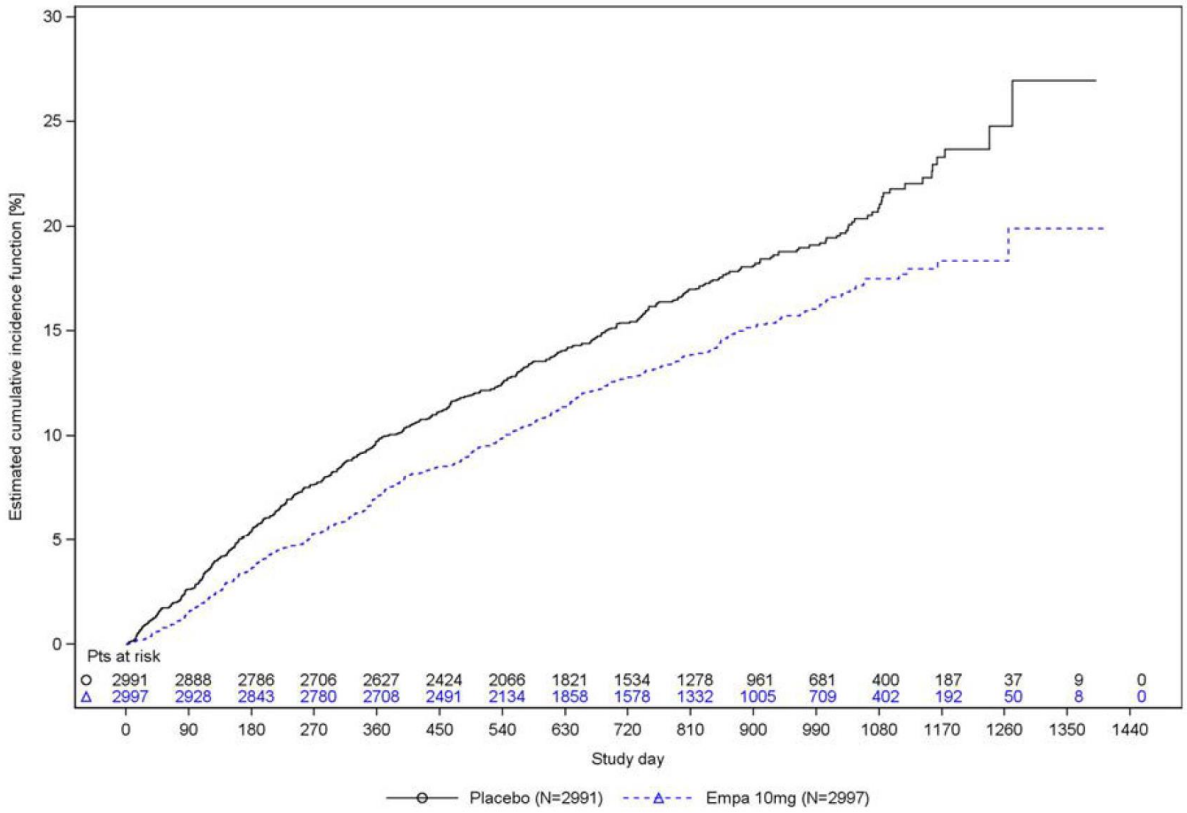
HFpEF patients with atrial fibrillation (46% to 60%), but the proportion of patients with hypertension (65% to 80%) was lower than in the trial. The EMPEROR-Preserved trial included 49.1% of patients with diabetes at baseline (randomisation was stratified by diabetes status with a minimum of 35% patients with diabetes planned for inclusion in the trial). The Australian study populations with HFmrEF/HFpEF included between 27% and 53% of patients with diabetes.

6.9 The submission argued that the subgroup analyses of the EMPEROR-Preserved trial demonstrated that both age and sex are not treatment effect modifiers and therefore any difference between the trial and the clinical setting are unlikely to be impactful. While the pre-specified subgroup analyses showed no treatment effect interactions, age and sex, along with NYHA class and the presence of comorbid conditions have been identified as prognostic factors in HFpEF. Any differences between the trial population and the Australian setting in terms of patient demographics and the prevalence of comorbid conditions may therefore result in differences in the absolute benefit of empagliflozin. The ESC noted that there were baseline differences between the EMPEROR-Preserved Trial and the proposed PBS population, but that these differences were bidirectional and, on balance, had no significant concerns regarding the applicability of the EMPEROR-Preserved trial to the PBS population.

## *Comparative effectiveness*

6.10 Figure 1 and Table 4 summarise the results of the primary composite outcome (time to first cardiovascular death or hospitalisation for heart failure) of the EMPEROR-Preserved trial.

**Figure 1: Time to first cardiovascular death or hospitalisation for HF (adjudicated), estimated cumulative incidence function (considering non-CV death as a competing risk) in the EMPEROR-Preserved trial (ITT)**




Source: Figure 2.5, p85 of the submission.
Abbreviations: CV, cardiovascular; HF, heart failure

**Table 4: Results for the primary composite outcome of time to first cardiovascular death or hospitalisation for HF (adjudicated) from the EMPEROR-Preserved trial (ITT)**

| Outcome | Empagliflozin N=2,997, n (%) | Placebo N=2,991, n (%) | Hazard ratio (95.03% CI)[a] |
|---|---|---|---|
| Composite of time to CV death or HHF [b] | 415 (13.8) | 511 (17.1) | **0.79 (0.69, 0.90)** |
| - HHF as the first event | 258 (8.6) | 352 (11.8) | - |
| - CV death as the first event | 156 (5.2) | 159 (5.3) | - |
| - both events on same day | 1 (<0.1) | 0 | - |

Source: Table 2.19, p85 of the submission.
Abbreviations: CV, cardiovascular; HHF, hospitalisation for heart failure; ITT, intention to treat.
[a] Hazard ratios <1 favour empagliflozin. Statistically significant results in bold. 95.03% CI based on reduced 2-sided α level of 0.0497 resulting from interim analysis.
[b] Cox regression model included factors age, baseline eGFR, region, baseline diabetes status, sex, baseline LVEF, and treatment.

6.11 Treatment with empagliflozin was associated with a statistically significant improvement in the primary composite endpoint of time to cardiovascular death, or hospitalisation for heart failure compared to placebo (hazard ratio: 0.79; 95% CI 0.69, 0.90), over a median duration of follow-up of 26 months. The submission noted that the hazard ratio falls within the range the PBAC has previously considered to be clinically meaningful for patients with LVEF ≤40%. However, the ESC noted that the absolute risk reduction in the primary composite endpoint (3.2% over a median

follow-up of 26 months; Table 4) was lower than for the HFrEF population for empagliflozin in EMPEROR-Reduced (5.3% over a median duration of follow-up of 16 months. Table 4, empagliflozin, PSD, November 2021 PBAC meeting). The ESC noted that this represented a more modest treatment effect in the HFmrEF/HFpEF population compared with the HFrEF population.

6.12 Table 5 summarises the results of the key secondary outcome, occurrence of adjudicated hospitalisation (first and recurrent) for heart failure. This outcome was evaluated with a joint frailty model that accounted for the dependence between recurrent hospitalisation for heart failure and cardiovascular death, and was based on all data up to the end of the planned treatment period from all randomised patients.

**Table 5: Results for the key secondary outcome of time to hospitalisation for HF (adjudicated) using a frailty model with a competing risk of CV death from the EMPEROR-Preserved trial (ITT)**

| Outcome | Empagliflozin N=2,997, n (%) | Placebo N=2,991, n (%) | Hazard ratio (95% CI)[a] |
|---|---|---|---|
| **Adjudicated HHF (first and recurrent)[b] (joint frailty model)** | | | |
| Number of HHF events, n | 407 | 541 | - |
| Patients with HHF events, n (%) | 259 (8.6) | 352 (11.8) | **0.73 (0.61, 0.88)** |
| patients with HHF then CV death | 63 (2.1) | 85 (2.8) | |
| patients with HHF only | 196 (6.5) | 267 (8.9) | |
| Patients with CV death only, n (%) | 156 (5.2) | 159 (5.3) | 0.89 (0.71, 1.12) |

Source: Table 2.20, p88 of the submission.

Abbreviations: CV, cardiovascular; HHF, hospitalisation for heart failure; ITT, intention to treat; SC, standard care.

[a] Hazard ratios <1 favour empagliflozin. Statistically significant results in bold.

[b] Joint frailty exponent (alpha) 1.02. Joint frailty model included factors age, region, sex, and baseline eGFR, diabetes status, LVEF.

6.13 The total number of hospitalisations for heart failure (first and recurrent) was lower in the empagliflozin arm (407 events) compared to the placebo arm (541 events). Treatment with empagliflozin statistically significantly reduced the risk of first and recurrent hospitalisation for heart failure compared to placebo (HR 0.73; 95% CI 0.61, 0.88). The hazard of recurrent HHF was positively correlated with that of CV death (indicated by a frailty exponent >0).

6.14 The rate of decline in eGFR over a median duration of follow up of 26 months was statistically significantly slower in patients treated with empagliflozin compared to placebo, with an estimated difference in slope of 1.363 per year (95% CI 1.064, 1.662). However, the composite outcome of time to first renal event showed no nominally significant difference between the empagliflozin (3.6% of patients with events) and placebo arms (3.7% of patients with events; hazard ratio 0.95, 95% CI 0.73, 1.24, see Table 6 below).

6.15 Table 6 summarises the results of exploratory cardiovascular and renal outcomes from the EMPEROR-Preserved trial.

**Table 6: Results for the exploratory cardiovascular and renal outcomes from the EMPEROR-Preserved trial (ITT)**

| Outcome | Empagliflozin N=2,997, n (%) | Placebo N=2,991, n (%) | Hazard ratio (95% CI)[a] |
|---|---|---|---|
| First adjudicated HHF | 259 (8.6) | 352 (11.8) | 0.71 (0.60, 0.83) |
| Adjudicated CV death | 219 (7.3) | 244 (8.2) | 0.91 (0.76, 1.09) |
| All-cause mortality | 422 (14.1) | 427 (14.3) | 1.00 (0.87, 1.15) |
| All cause hospitalisation (first and recurrent) | 934 (31.2) | 1004 (33.6) | 0.93 (0.85, 1.01) |
| Composite renal endpoint [b] | 108 (3.6) | 112 (3.7) | 0.95 (0.73, 1.24) |

Source: Table 2.22, p91; Table 2.23, p93; Table 2.24, p94; Table 2.25, p95; Table 2.26, p97 of the submission.
Abbreviations: CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalisation for heart failure; ITT, intention to treat.
[a] Hazard ratios <1 favour empagliflozin
[b] Composite of time to first event of (i) chronic dialysis (≥ 2 times/week for at least 90 days); (ii) renal transplant, (iii) sustained reduction in eGFR from baseline of ≥40%; (iv) sustained eGFR <15 mL/min/1.73 $m^2$ from baseline ≥30 mL/min/1.73 $m^2$, or <10 mL/min/1.73 $m^2$ from baseline <30 mL/min/1.73 $m^2$.

6.16 Point estimates for the exploratory outcome of first adjudicated hospitalisation for heart failure favoured empagliflozin compared to placebo, but given the outcome was exploratory, any significant difference should be considered nominal only. Similar proportions of cardiovascular death, all-cause mortality, all-cause hospitalisation, and the composite renal endpoint were reported in both treatment arms.

6.17 The submission stated that the cumulative incidence of adjudicated CV death suggests a decrease in the risk of CV death in the empagliflozin arm with clear separation of curves after 720 days, but noted that the EMPEROR-Preserved trial was not powered to detect differences in mortality outcomes. The submission also stated that the event rate for cardiovascular death was low over the median 26 months of follow-up (3.8 per 100 patient years in the placebo arm of the trial), and that only 55% of deaths occurring during the trial were attributed to cardiovascular causes. The low event rate coupled with a greater competing risk of non-CV deaths may have limited the statistical power of EMPEROR-Preserved to detect a significant treatment effect on cardiovascular mortality (McDowell and Docherty 2022). The corresponding incidence rate of cardiovascular death in the EMPEROR-Reduced trial was 8.1 per 100 patient years, with 76% of all deaths attributed to cardiovascular causes. The ESC advised that, unlike in HFrEF, it was not confident that a longer follow up period was likely to show any significant benefit in cardiovascular deaths in this population.

6.18 The PBAC noted the pre-PBAC response referred to a recently published meta-analysis that pooled data from EMPEROR-Preserved and DELIVER2. The authors found that SGLT2 inhibitors reduced CV mortality by 12% with nominal significance and no statistically significant heterogeneity (HR 0.88; 95% CI: 0.77,1.00).

6.19 Treatment with empagliflozin compared to placebo was associated with nominally significantly greater improvements in the KCCQ overall summary score, clinical

[2]Vaduganathan M, et al. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. Lancet. 2022 Sep 3;400(10354):757-767.

summary score and total summary score from baseline to Week 52. Improvements in the KCCQ clinical summary scores were demonstrated from week 12 of treatment in both treatment.

6.20 The submission noted that a clinically meaningful improvement in KCCQ clinical summary score (≥5 points) occurred more frequently in the empagliflozin treatment arm (41.7% of patients) compared to placebo (38.7%; odds ratio 1.120; 95% CI 0.996, 1.259), and fewer patients in the empagliflozin treatment arm (30.3%) reported a clinically meaningful decrease in KCCQ score (≥5 points) compared to placebo (33.9%; odds ratio 0.852; 95% CI: 0.759, 0.957; Tables 15.2.3.6:11 and 15.2.3.6:12, pp538-539 of the EMPEROR-Preserved CSR).

6.21 Health-related quality of life was assessed using the EQ-5D-5L in the EMPEROR-Preserved trial, with summary scores reported in the statistical analysis for the submission's economic model. Similar results were observed between treatment arms, with scores remaining stable over time.

6.22 The results of pre-specified subgroup analyses for the primary outcome of time to first cardiovascular death or hospitalisation for heart failure were generally consistent with the result reported for the ITT population. There were no nominally significant differences between subgroups in tests for treatment effect.

6.23 The submission summarised the results of a pooled analysis of patient-level data from the EMPEROR-Reduced and EMPEROR-Preserved trials (Butler 2021) that evaluated the effect of empagliflozin on heart failure outcomes across the full range of left ventricular ejection fraction. In a post hoc analysis, 9,718 patients were divided into six LVEF groups: <25%, 25-34%, 35-44%, 45-54%, 55-64% and ≥65%. There were clear differences in baseline patient characteristics across the spectrum of LVEF – patients with higher LVEF were more likely to be older and female, and with impaired renal function and lower levels of natriuretic peptides. The prevalence of comorbid diseases also differed, with increasing LVEF associated with decreasing prevalence of ischaemic heart disease but increasing prevalence of atrial fibrillation.

6.24 Results of the pooled analysis for heart failure outcomes and health status are summarised in Table 7.

**Table 7: Efficacy of empagliflozin on heart failure outcomes and health status in EMPEROR-Reduced and EMPEROR-Preserved, by LVEF**

| Outcome measure[a] | Left ventricular ejection fraction range | | | | | |
|---|---|---|---|---|---|---|
| | **<25%<br>EMP n=476<br>PBO n=523** | **25-34%<br>EMP n=1,115<br>PBO n=1,115** | **35-44%<br>EMP n=659<br>PBO n=613** | **45-54%<br>EMP n=1,111<br>PBO n=1,149** | **55-64%<br>EMP n=1,071<br>PBO n=1,021** | **≥65%<br>EMP n=428<br>PBO n=437** |
| HHF or CV death | 0.77<br>(0.60, 0.98) | 0.72<br>(0.59, 0.87) | 0.82<br>(0.63, 1.05) | 0.74<br>(0.61, 0.91) | 0.78<br>(0.62, 0.97) | 0.98<br>(0.68, 1.40) |
| First HHF | 0.73<br>(0.55, 0.96) | 0.63<br>(0.50, 0.78) | 0.72<br>(0.52, 0.98) | 0.66<br>(0.50, 0.86) | 0.70<br>(0.53, 0.92) | 1.05<br>(0.70, 1.58) |
| Total HHF | 0.74<br>(0.50, 1.07) | 0.67<br>(0.51, 0.87) | 0.79<br>(0.55, 1.12) | 0.56<br>(0.42, 0.76) | 0.81<br>(0.59, 1.10) | 1.03<br>(0.67, 1.60) |
| Cardiovascular death | 0.93<br>(0.65, 1.32) | 0.95<br>(0.72, 1.24) | 1.07<br>(0.76, 1.51) | 0.77<br>(0.58, 1.02) | 0.99<br>(0.70, 1.40) | 0.83<br>(0.47, 1.45) |
| KCCQ Clinical Summary Score change from baseline to 52 weeks | | | | | | |
| Number of patients | EMP n=319<br>PBO n=338 | EMP n=744<br>PBO n=743 | EMP n=482<br>PBO n=444 | EMP n=906<br>PBO n=928 | EMP n=898<br>PBO n=854 | EMP n=363<br>PBO n=368 |
| Absolute change (95%CI) | 3.01<br>(0.68, 5.33) | 0.92<br>(–0.62, 2.46) | 1.82<br>(–0.16, 3.81) | 1.59<br>(0.16, 3.01) | 1.95<br>(0.48, 3.41) | 0.26<br>(–2.01, 2.52) |

Source: Table 3, p423; Figure 3, p422 of Butler 2021.

Abbreviations: CV, cardiovascular; EMP, empagliflozin; HHF, hospitalisation for heart failure; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score; PBO, placebo

[a] All outcomes are hazard ratios with 95% confidence intervals, with the exception of KCCQ scores which are absolute differences with 95% confidence intervals

6.25 Results of the pooled analysis suggested a consistent benefit across LVEF groups of empagliflozin over placebo for the primary outcome of hospitalisation for heart failure or cardiovascular death, and time to first hospitalisation for heart failure. There was no significant treatment effect interaction between ejection fraction and the effect of empagliflozin on the primary composite endpoint, based on the pooled analysis (p-interaction = 0.30) or EMPEROR-Preserved data only (p-interaction = 0.43). There appeared to be attenuation of effect for patients with LVEF of 65% or greater for all heart failure hospitalisation outcomes. The study authors noted that there were small patient numbers in this group (less than 10% of the entire patient population and number of events), and patients in the group appeared to be mostly older, hypertensive women with low incidence of hospitalisation for heart failure during the course of follow-up. The study authors speculated that these patients may have had symptoms of dyspnoea that were less related to heart failure but more attributable to an atrial arrhythmia or other condition.

## *Comparative harms*

6.26 Table 8 summarises the results of the key safety outcomes for the EMPEROR-Preserved trial.

**Table 8: Summary of key adverse events in the EMPEROR-Preserved trial (treated set)**

| Adverse events, n (%) | Empagliflozin (N=2,996), n (%) | Placebo (N=2,989), n (%) |
|---|---|---|
| Patients with any adverse events | 2,574 (85.9) | 2,585 (86.5) |
| Severe adverse events | 786 (26.2) | 851 (28.5) |
| Serious adverse events | 1,436 (47.9) | 1,543 (51.6) |
| Drug-related adverse events | 494 (16.5) | 413 (13.8) |
| Adverse events leading to treatment discontinuation | 571 (19.1) | 551 (18.4) |
| Adverse events resulting in death | 287 (9.6) | 297 (9.9) |
| Adverse events requiring or prolonging hospitalisation | 1,106 (36.9) | 1,182 (39.5) |

Source: Table 2.27, p100 of the submission.

6.27 The proportions of patients reporting adverse events were similar between treatment arms, with more patients treated with empagliflozin reporting drug related adverse events, and slightly more patients treated with placebo reporting serious adverse events and adverse events requiring or prolonging hospitalisation.

6.28 The most common adverse events of special interest reported in empagliflozin-treated patients were acute renal failure (12.1%, placebo 12.8%), volume depletion (11.9%, placebo 9.6%), hypotension (10.4%, placebo 8.6%) and urinary tract infection (9.9%, placebo 8.1%). More genital infections were reported in empagliflozin treated patients than placebo (2.2% versus 0.7%), although absolute numbers of infections were low in both groups.

6.29 Overall, the safety profile was consistent with the known safety profile of empagliflozin in the treatment of type 2 diabetes and HFrEF, with no unexpected safety signals detected in the EMPEROR-Preserved trial. The ESC considered that the safety profile of empagliflozin is well understood.

## *Benefits/harms*

6.30 On the basis of the direct evidence presented in the submission, for every 100 patients treated with empagliflozin plus standard care in comparison with placebo plus standard care over a duration of follow-up of 26 months:

- Approximately 3 fewer patients would be hospitalised for heart failure.
- There would be no difference in the number of people who die from heart-related causes.
- Approximately 3 additional patients may experience a drug-related adverse event.

## *Clinical claim*

6.31 The submission described empagliflozin plus standard care as superior in terms of effectiveness, and non-inferior in terms of safety compared to placebo plus standard care, in the treatment of patients with chronic HFmrEF/HFpEF.

6.32 The therapeutic conclusion presented in the submission was adequately supported by the evidence presented in Section 2 of the submission. However the evaluation

considered the applicability of the EMPEROR-Preserved results to the Australian patient population was uncertain, given differences in risk factors of age and sex, and limited Australian data to determine the applicability of the trial results to the requested population. The ESC noted that limited Australian data were available, however considered that, on balance, there were no significant concerns regarding the applicability of the EMPEROR-Preserved trial to the PBS population.

6.33 The PBAC considered that the claim of superior comparative effectiveness was adequately supported by the data.

6.34 The PBAC considered that the claim of non-inferior comparative safety was adequately supported by the data.

## *Economic analysis*

6.35 The submission presented a modelled economic evaluation of empagliflozin plus standard care versus standard care alone, in patients with HFmrEF/HFpEF. The economic analysis was based on the results of the EMPEROR-Preserved trial, with additional modelled data. The type of economic evaluation presented was a cost-effectiveness/cost-utility analysis.

**Table 9: Key components of the economic evaluation**

| Component | Summary |
|---|---|
| Treatments | Empagliflozin plus standard care versus standard care alone |
| Time horizon | 15 years in the model base case versus median follow-up of 26.2 months in the EMPEROR-Preserved trial |
| Outcomes | Life years; quality adjusted life years |
| Methods used to generate results | Markov state transition model |
| Health states | 4 health states based on KCCQ-CSS quartiles (0 to <55.7, 55.7 to <74.0, 74.0 to <88.0, 88.0 to 100; where a higher score is better) and 2 death states (CV and non-CV) |
| Cycle length | One month |
| Transition probabilities | KCCQ-CSS transitions for 3 time periods (baseline to Week 12, Week 12 to Week 32, Week 32 to Week 52) were based on individual patient data from EMPEROR-Preserved. Transition probabilities from Week 32 to Week 52 were used for the remaining time horizon (to 15 years).<br>CV death transitions were based on Kaplan Meier time to CV death curves from EMPEROR-Preserved over 30 months, extrapolated to 15 years based on a Weibull function, with treatment and KCCQ-CSS quartiles as covariates.<br>Non-CV death transitions were derived from estimates of all-cause mortality minus estimates of CV mortality. All-cause mortality was based on a Weibull function fitted to Kaplan Meier time to all-cause mortality curves from EMPEROR-Preserved, with KCCQ-CSS quartiles as covariates, extrapolated to 15 years. A correction was included to ensure that the monthly probability of non-CV death was not smaller than that of the Australian general population (adjusted to remove CV death).<br>Monthly probabilities of treatment discontinuation in the empagliflozin arm were based on a generalised gamma distribution fitted to the Kaplan Meier time to treatment discontinuation |

| Component | Summary |
|---|---|
| | curve (censored for death) from EMPEROR-Preserved, with KCCQ-CSS quartiles as covariates, extrapolated to 15 years.<br>Monthly probabilities of heart failure hospitalisation were derived using a Poisson model fitted to the observed data from EMPEROR-Preserved with treatment and KCCQ-CSS quartiles as covariates. Probabilities were assumed to remain constant over time.<br>The monthly probabilities of adverse events were derived from the rate per 100 patient years of adverse events of special interest and specific adverse events from the EMPEROR-Preserved trial.<br>52.8% of incremental costs and 75.1% of incremental QALYs are accrued in the extrapolated period beyond 26 months. |
| Costs | The cost of empagliflozin was based on the proposed DPMQ and assumed 100% adherence.<br>The cost of standard care was based on the distribution of use of heart failure medicine classes in EMPEROR-Preserved, the recommended dose for each medicine based on its PI, the DPMQ and pack size from the PBS Schedule; and assumed 100% adherence.<br>Disease management costs were based on estimates of resource use by NYHA class (Ford 2012) which were assumed to apply to KCCQ quartiles (e.g. NYHA class IV corresponds to KCCQ-CSS quartile I), with unit costs based on MBS items.<br>Heart failure hospitalisation costs were based on AR-DRG costs for heart failure.<br>Cardiovascular death costs were based on AR-DRG costs for heart failure, stroke and myocardial infarction.<br>Adverse event costs were weighted by severity (based on data from EMPEROR-Preserved), with various AR-DRG costs applied for serious adverse events and the cost of a level B GP visit used for non-serious adverse events. |
| Health related quality of life | EQ-5D-5L scores from EMPEROR-Preserved were mapped to EQ-5D-3L scores using the methodology outlined in van Hout 2012, using the UK value set.<br>KCCQ-CSS health state utilities were derived from a linear mixed regression equation fitted to EQ-5D-3L data derived from EMPEROR-Preserved. Utilities were adjusted so that utilities did not exceed the utility of the UK general population aged 70 to 79 (KCCQ-CSS quartile 4, 0.7230; quartile 3, 0.6758; quartile 2, 0.6145; quartile 1, 0.5328).<br>Disutilities of heart failure hospitalisation were also derived from the linear mixed regression equation fitted to data from EMPEROR-Preserved. Time-varying indicators were collected at the time of utility measurement to capture short- and longer-term effects of heart failure hospitalisations on utilities (heart failure hospitalisation disutility <1 month, -0.0468; 1 to <2 months, -0.0577; 2 to <4 months, -0.0424; 4 to <12 months -0.0183).<br>Adverse event disutilities were derived from EMPEROR-Preserved and published sources (Sullivan 2006, Sullivan 2016, Peasgood 2016) ranging from to -0.0022 for a hypoglycaemic event to -0.156 for bone fracture); assumed to apply for 1 month. |
| Discount rate | 5% for costs and benefits |
| Software | Microsoft Excel |

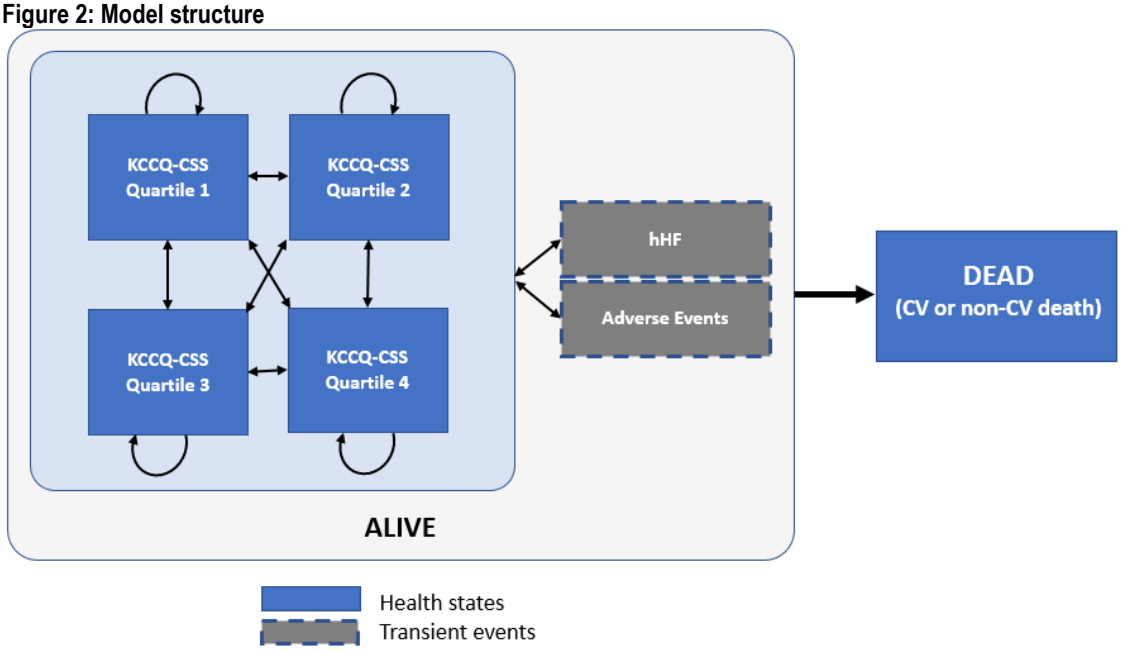
Source: Table 3.1, p135 of the submission, Sections 3.3 to 3.6 of the submission
Abbreviations: AR-DRG, Australian Refined Diagnosis Related Group; CV, cardiovascular; DPMQ, dispensed price for maximum quantity; GP, general practitioner; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; MBS, Medicare Benefits Schedule; NYHA, New York Heart Association; PBS, Pharmaceutical Benefits Scheme; PI, product information

6.36 The submission nominated a 15-year time horizon for the economic model on the basis that it provides a reasonable balance between the estimation of the costs and consequences associated with each treatment arm and the uncertainty associated with the extrapolation beyond the follow-up of EMPEROR-Preserved (with a median duration of follow-up of 26.2 months). In its consideration of the November 2021

empagliflozin HFrEF submission, the PBAC considered that, although the nominated 15-year time horizon may not be sufficient to capture the lifetime costs and consequences associated with empagliflozin plus standard care versus standard care, a longer time horizon would be associated with additional uncertainty given the extrapolation of outcomes based on a median follow-up of 16 months in the EMPEROR-Reduced trial (para 6.47, empagliflozin, PSD, November 2021 PBAC meeting). In the current model, 87% of patients aged 71.9 years at baseline had died after 15 years; compared with 90% of patients aged 66.7 years at baseline in the November 2021 empagliflozin HFrEF model.

6.37 The model has the same structure as the model used in the November 2021 empagliflozin HFrEF submission, as illustrated in Figure 2.

**Figure 2: Model structure**




Source: Figure 3.4, p167 of the submission
Abbreviations: CV, cardiovascular; hHF, hospitalisation due to heart failure; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score

6.38 Subjects begin the model in one of the four KCCQ-CSS quartile health states. During each one-month cycle, subjects may remain in their KCCQ-CSS quartile health state, move to another KCCQ-CSS quartile health state, or die from cardiovascular or non-cardiovascular causes. During each cycle, subjects can experience hospitalisation due to heart failure or treatment-related adverse events. Subjects in the empagliflozin arm may discontinue drug treatment in each cycle. The model applies higher rates of heart failure hospitalisation, and CV and non-CV mortality to patients with poorer KCCQ-CSS scores (based on quartiles).

6.39 In the model, heart failure hospitalisations are associated with a cost and disutility, but do not alter health state transitions and do not affect mortality rates, which is

unlikely to reflect the disease pathway. The ESC previously considered that, while the impact of heart failure hospitalisation on health state transitions and mortality may be implicitly captured within the trial period, this was less likely over the extrapolated period (para 6.50, Empagliflozin PSD, November 2021 PBAC meeting). The PSCR stated that although HHF may impact heath state transitions and mortality rates, incorporating HHF as a separate health state would have significantly increased the complexity of the model and relied on limited data (i.e., 540 and 407 HHF events were observed for placebo plus SC and empagliflozin plus SC treatment, respectively) thereby increasing uncertainty. The PSCR also stated that any HHF that resulted in a change in health state or death in EMPEROR-Preserved is implicitly captured in the KCCQ-based health state transition matrices and/or the mortality equations. The ESC acknowledged that it may not be feasible to add a separate health state for HHF, however the impact of HHF events could potentially be included in the calculation of the transition probabilities which may better reflect the disease pathway.

6.40 The submission stated that the health states were defined based on KCCQ-CSS quartiles, rather than the more commonly used NYHA functional classification because the KCCQ score is an established and prognostically important measure of health status in patients with heart failure. The submission claimed that the reliability, validity and responsiveness of the KCCQ have been independently established in heart failure, including in patients with HFpEF, and that defining health states based on KCCQ score provides a patient-centred assessment of disease burden, allowing the impact of disease severity on quality of life to be captured more accurately in the health state utilities and risk of events, such as heart failure hospitalisation.

6.41 The ESC considered that the results of the economic model were uncertain due to several concerns as noted by the evaluation. The key concerns were:

- The majority of incremental costs (52.8%) and incremental QALYs (75.1%) in the economic model were accrued in the extrapolated period beyond 26 months (Table 9).
- The KCCQ-CSS transitions for 3 time periods (baseline to Week 12, Week 12 to Week 32, Week 32 to Week 52) were based on individual patient data from EMPEROR-Preserved, and that transition probabilities from Week 32 to Week 52 were used for the remaining time horizon (to 15 years; Table 9). The ESC considered this approach was unlikely to adequately capture the progressive nature of the condition in later years.
- The CV death transitions were based on Kaplan Meier time to CV death curves from EMPEROR-Preserved over 30 months, extrapolated to 15 years based on a Weibull function, with treatment and KCCQ-CSS quartiles as covariates; Table 9). The ESC considered that inclusion of treatment as a covariate was not appropriate given there was no significant difference seen in mortality between the treatment arms. The ESC noted the impact could not be tested

in sensitivity analyses due to the model design, and considered this was inappropriate as it hindered assessment of the key drivers. The ESC considered that the modelled survival benefit for empagliflozin should be removed from the model.

- The non-CV death transitions were derived from estimates of all-cause mortality minus estimates of CV mortality and that a correction was included to ensure that the monthly probability of non-CV death was not smaller than that of the Australian general population (Table 9). The ESC considered this approach was associated with a high degree of uncertainty.
- The monthly probabilities of heart failure hospitalisation were derived using a Poisson model fitted to the observed data from EMPEROR-Preserved with treatment and KCCQ-CSS quartiles as covariates and that probabilities were assumed to remain constant over time (Table 9). The ESC considered this approach was unlikely to adequately capture the progressive nature of the condition in later years, for example the model did not explicitly reflect a relationship between HHF events and disease progression or death.
- UK value sets were used for generation of health related quality of life inputs, rather than Australian value sets (Table 9).

6.42 The submission presented a sensitivity analysis assessing the impact of using NYHA class health states instead of KCCQ-CSS quartiles. The sensitivity analysis used individual patient data from EMPEROR-Preserved to derive monthly transitions between NYHA class health states.

6.43 Key drivers of the economic model are summarised in Table 10 below.

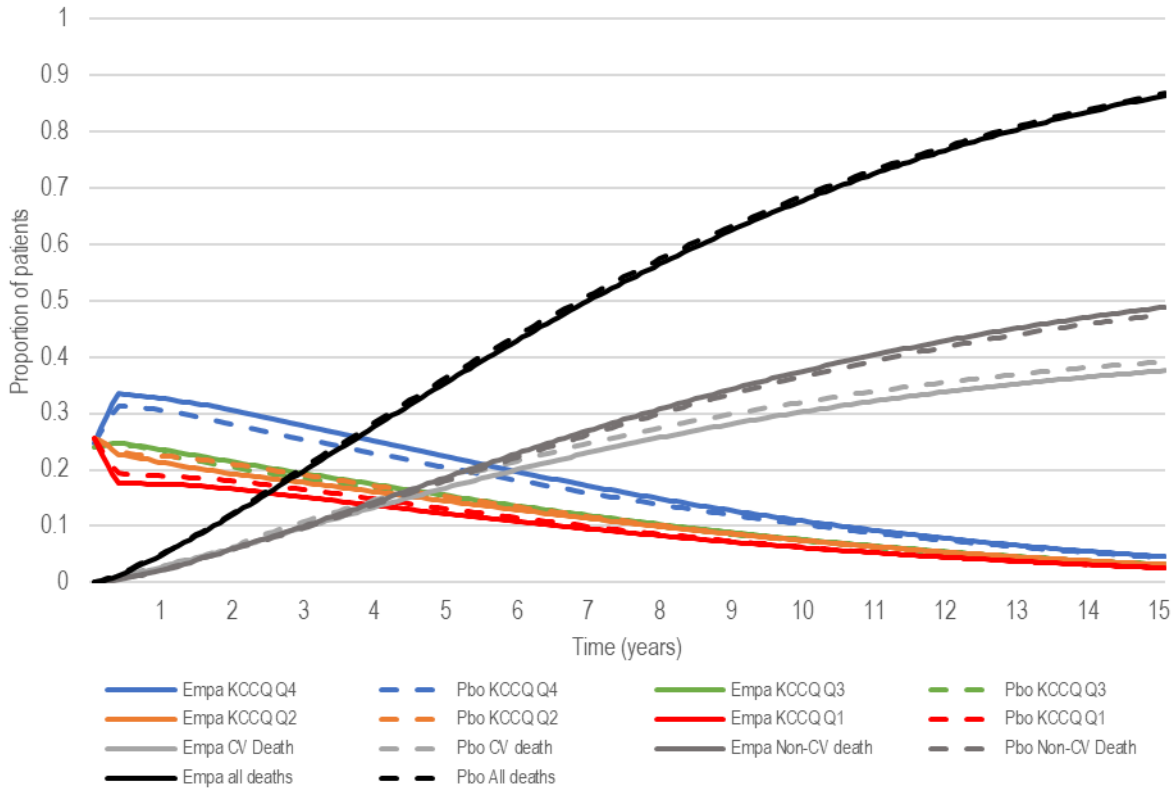
**Table 10: Key drivers of the model**

| Description | Method/Value | Impact |
|---|---|---|
| Modelled mortality benefit | The model assumes differences in time to cardiovascular death favouring empagliflozin that are not consistent with the available clinical data, although numerical results favoured empagliflozin (see Table 6 above). The ESC noted that results from the DELIVER trial, in dapagliflozin, also do not show a mortality benefit over a longer median duration of follow up than in the HFrEF studies. The ESC advised no mortality benefit should be included in the model.<br>In the model, a cardiovascular mortality benefit for empagliflozin is generated from improved survival within each KCCQ-CSS health state, as well as from higher proportions of patients in the empagliflozin arm transitioning to KCCQ-CSS quartiles representing improved health status which have lower mortality (and lower proportions transitioning to lower health status quartiles with higher mortality) compared with the placebo arm. No supportive data were presented to support a survival benefit with empagliflozin (such as a meta-analysis of EMPEROR-Preserved and EMPEROR-Reduced trials), or to support the modelled relationship between KCCQ-CSS quartiles and survival.<br>The impact of no survival benefit associated with empagliflozin treatment could not be adequately tested during the evaluation due to the model structure with estimates of cardiovascular mortality curves derived separately for KCCQ-CSS health states. | High, favours empagliflozin |
| KCCQ-CSS quartile health state transitions | The model assumes that transition probabilities between KCCQ-CSS quartile health states, derived from individual patient data from EMPEROR-Preserved between 9 and 12 months, are constant from month 9 to the end of the 15 year model time horizon. The analysis of individual patient data indicates that patients in both treatment arms experience initial improvement in health status, followed by stabilisation. It is unclear whether transitions derived from the 9-12 month period adequately reflect longer term health outcomes in a progressive disease. | Unclear |
| QALY loss associated with hospitalisation for heart failure | The disutility associated with heart failure hospitalisation, derived from EMPEROR-Preserved EQ-5D data, was assessed at different timepoints to capture short-and long-term effects. In calculating the total QALY loss associated with heart failure hospitalisations, the submission assumed that the disutilities derived from the linear regression equation represent QALY losses over a one month period. To calculate the QALY loss over a 12 month period, the disutilities associated with each time period were multiplied by the number of months in the time period (e.g. the disutility for 2 to <4 months was multiplied by 2 months) rather than the proportion of a year spent in the health state (e.g. ×2/12 months). This approach differed to the approach used to calculate the QALY loss associated with adverse events, which multiplied the disutilities by 1/12 to derive the QALY loss over a one-month period. The assumption that estimates from the linear regression equation represented monthly QALY losses for heart failure hospitalisation results in implausibly large disutilities for heart failure hospitalisation (disutilities of -0.562 and -0.692 in the first 2 months post-hospitalisation) that are inconsistent with the published literature. As a consequence, the estimated monthly QALY loss for heart failure hospitalisation was treated as a calculation error during the evaluation. The ESC agreed with the evaluation and noted that the submission QALY loss lacked face validity for a single hospital event and the evaluation calculation aligned more closely with a recently published systematic review (Di Tanna 2021[3]). | Moderate, favours empagliflozin |

Source: Constructed during the evaluation with reference to Section 3 of the submission and 'Att_8_Jardiance (empagliflozin) - HF with LVEF more than 40 - CEA' spreadsheet provided with the submission

6.44 Figure 3 below presents the model traces for the empagliflozin plus standard care and placebo plus standard care arms.

**Figure 3: Model trace for empagliflozin plus standard care and placebo plus standard care**




Source: Constructed during the evaluation using 'Att_8_Jardiance (empagliflozin) – HF with LVEF more than 40 - CEA' spreadsheet provided with the submission

Abbreviations: CV, cardiovascular; Empa, empagliflozin plus standard care; KCCQ Q1-4, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score Quartiles 1 to 4; Pbo, placebo plus standard care

6.45 The model trace indicated that empagliflozin was associated with a survival benefit, due to a reduction in cardiovascular deaths. This was inconsistent with the results of the EMPEROR-Preserved trial, which suggest no difference in mortality between treatments (see Table 6 above). There were higher proportions of patients in the KCCQ-CSS quartile 4 health state, and lower proportions in the KCCQ-CSS quartile 1 health state in the empagliflozin plus standard care arm compared to placebo plus standard care, indicating better health status over the model duration. After 15 years, 87% of patients aged 71.9 years at baseline had died.

6.46 The model estimates that on average, patients treated with empagliflozin plus standard care experienced 0.55 heart failure hospitalisations, compared with 0.63 hospitalisations in patients treated with standard care alone over 15 years.

[3] Di Tanna GL, Urbich M, Wirtz HS, Potrata B, Heisen M, Bennison C, Brazier J, Globe G. Health State Utilities of Patients with Heart Failure: A Systematic Literature Review. Pharmacoeconomics. 2021 Feb;39(2):211-229. doi: 10.1007/s40273-020-00984-6. Epub 2020 Nov 30. PMID: 33251572; PMCID: PMC7867520.

6.47 Based on the extrapolated time to treatment discontinuation curve, the model estimates that 81.0% of empagliflozin plus standard care patients remain on empagliflozin treatment at 1 year, which decreases to 29.1% at 5 years (45.5% of those remaining alive) and 4.5% at 10 years (14.3% of those remaining alive). At the end of the model (at 15 years), 0.3% of patients remain on empagliflozin (2.5% of those remaining alive).

6.48 The results of the stepped economic evaluation are summarised in Table 11 below. Step 1 of the submission's stepped economic evaluation was based on a 42 month duration. This is longer than the median duration of follow-up of the EMPEROR-Preserved trial (26 months), and the point at which observed time-to-event data are used in extrapolations of cardiovascular mortality and time to treatment discontinuation (30 months). The submission stated that 42 months represents the last observed data point for AC and CV morality as well as TTD in EMPEROR-Preserved. During the evaluation, Step 3 (incorporating non-drug costs) was divided into four sub-steps (disease management costs, heart failure hospitalisation costs, cardiovascular death costs, adverse event costs) and Step 4 (incorporating utilities) was divided into three sub-steps (health state utilities, heart failure hospitalisation disutility, adverse event disutility) to more clearly identify the key components of the economic model.

**Table 11: Results of the stepped economic evaluation**

| Step and component | Empagliflozin+SC | Placebo+SC | Increment |
|---|---|---|---|
| **Step 1: Modelled analysis based on Kaplan-Meier overall survival curves by KCCQ-CSS quartile from EMPEROR-Preserved over 42 months and including drug costs only** | | | |
| Costs ($) | [redacted] | $2,069 | [redacted] |
| Life years | 2.9584 | 2.9556 | 0.0028 |
| Incremental cost per life year gained | | | $[redacted][1] |
| **Step 2: Time horizon extended to 15 years using extrapolated all-cause and cardiovascular mortality curves, with correction to ensure that mortality is not smaller than that of the Australian general population** | | | |
| Costs ($) | [redacted] | $4,227 | [redacted] |
| Life years | 6.1064 | 6.0392 | 0.0672 |
| Incremental cost per life year gained | | | $[redacted][2] |
| **Step 3: Disease management heart failure hospitalisation, CV death and adverse event costs included** | | | |
| **Step 3a: disease management costs included** | | | |
| Costs ($) | [redacted] | $8,711 | [redacted] |
| Life years | 6.1064 | 6.0392 | 0.0672 |
| Incremental cost per life year gained | | | $[redacted][2] |
| **Step 3b: heart failure hospitalisation costs included** | | | |
| Costs ($) | [redacted] | $13,100 | [redacted] |
| Life years | 6.1064 | 6.0392 | 0.0672 |
| Incremental cost per life year gained | | | $[redacted][3] |
| **Step 3c: CV death costs included** | | | |
| Costs ($) | [redacted] | $16,066 | [redacted] |
| Life years | 6.1064 | 6.0392 | 0.0672 |
| Incremental cost per life year gained | | | $[redacted][3] |
| **Step 3d: adverse event costs included** | | | |
| Costs ($) | [redacted] | $22,799 | [redacted] |
| Life years | 6.1064 | 6.0392 | 0.0672 |
| Incremental cost per life year gained | | | $[redacted][3] |
| **Step 4: Utilities applied to time in health states, disutilities applied for heart failure hospitalisation, adverse events** | | | |
| **Step 4a: utilities applied to time in health states** | | | |
| Costs ($) | [redacted] | $22,799 | [redacted] |
| QALYs | 3.9745 | 3.9079 | 0.0666 |
| Incremental cost per QALY gained | | | $[redacted][3] |
| **Step 4b: disutility applied for heart failure hospitalisation** | | | |
| Costs ($) | [redacted] | $22,799 | [redacted] |
| QALYs | 3.8267 | 3.7382 | 0.0885 |
| Incremental cost per QALY gained | | | $[redacted][4] |
| **Step 4c: disutilities applied for adverse events** | | | |
| Costs ($) | [redacted] | $22,799 | [redacted] |
| QALYs | 3.8212 | 3.7330 | 0.0882 |
| Incremental cost per QALY gained | | | $[redacted][4] |

Source: Table 3.27, p233 of the submission

Abbreviations: CV, cardiovascular; QALY, quality adjusted life years; SC, standard care

*The redacted values correspond to the following ranges:*

[1] *$555,000 to < $655,000/QALY gained*

[2] *$35,000 to < $45,000/QALY gained*

[3] *$25,000 to < $35,000/QALY gained*

[4] *$15,000 to < $25,000/QALY gained*

6.49 The extrapolation of outcomes beyond the clinical trial duration, the inclusion of heart failure hospitalisation costs and the inclusion of a disutility associated with heart failure hospitalisation had the largest impacts on the stepped economic evaluation.

6.50 Based on the modelled economic evaluation, treatment with empagliflozin plus standard care was associated with an incremental cost per QALY gained of $15,000 to < $25,000 compared to standard care alone for the treatment of HFmrEF/HFpEF.

6.51 On average, for every HFmrEF/HFpEF patient treated with empagliflozin plus standard care versus placebo plus standard care and followed up for 15 years, the (undiscounted) economic model estimates that there would be:

- Additional empagliflozin and standard care costs of $2,825 and additional costs of treating adverse events of $112.
- Additional survival of 1.14 months, associated with additional disease management costs ($34) and a reduction in the costs associated with cardiovascular death ($159).
- An additional 2.96 months spent in health states with higher quality of life (KCCQ-CSS quartiles 3 and 4), and 1.82 fewer months spent in health states with lower quality of life (KCCQ-CSS quartiles 1 and 2).
- A reduction of 0.07 heart failure hospitalisations (7 events per 100 patients), which would be associated with a reduction in hospitalisation costs ($791), and improved quality of life.

6.52 The results of key sensitivity analyses are summarised in Table 12 below. Results were not sensitive to the choice of parametric function used to inform cardiovascular mortality and treatment discontinuation, the inclusion of adverse event costs and disutilities, and disease management costs.

**Table 12: Results of sensitivity analyses**

| Analyses | Incremental cost $ | Incremental QALYs | ICER $ | % change from base case |
|---|---|---|---|---|
| **Base case** | [redacted] | **0.0882** | [redacted]1 | **-** |
| **Discount rate (base case 5% costs and outcomes)** | | | | |
| - 0% costs and outcomes | [redacted] | 0.1127 | [redacted]1 | -9% |
| - 3.5% costs and outcomes | [redacted] | 0.0945 | [redacted]1 | -3% |
| **Time horizon (base case 15 years)** | | | | |
| - 5 years | [redacted] | 0.0488 | [redacted]2 | 39% |
| - 10 years | [redacted] | 0.0771 | [redacted]1 | 9% |
| - 20 years | [redacted] | 0.0917 | [redacted]1 | -3% |
| **Health states (base case health states based on KCCQ-CSS quartiles; transitions based on EMPEROR-Preserved individual patient data)** | | | | |
| - empagliflozin transitions set equal to placebo transitions | [redacted] | 0.0272 | [redacted]3 | 212% |
| - placebo transitions set equal to empagliflozin transitions | [redacted] | 0.0279 | [redacted]3 | 215% |
| - health states based on NYHA class | [redacted] | 0.0812 | [redacted]1 | 11% |

| Analyses | Incremental cost $ | Incremental QALYs | ICER $ | % change from base case |
|---|---|---|---|---|
| **Heart failure hospitalisation rate (base case derived using Poisson model fitted to EMPEROR-Preserved data; monthly probabilities vary by KCCQ-CSS state and treatment)** | | | | |
| - constant monthly probability based on EMPEROR-Preserved (empagliflozin 0.53%; placebo 0.70%)[a] | [redacted] | 0.0871 | [1] | 3% |
| Halve incremental difference between empagliflozin and placebo | | 0.0783 | [2] | 28% |
| **Non-CV mortality (base case all-cause mortality based on a Weibull function fitted to KM data and extrapolated; no empagliflozin treatment effect; correction applied to ensure non-CV mortality exceeds general population mortality adjusted for CV mortality)** | | | | |
| - exponential function | [redacted] | 0.0966 | [1] | -4% |
| - Gompertz function | | 0.0640 | [2] | 20% |
| - lognormal function | | 0.1053 | [1] | -9% |
| - loglogistic function | | 0.0887 | [1] | 1% |
| - generalised gamma | | 0.0869 | [1] | 0% |
| - KM data used over 30 months; extrapolated using a Weibull function | | 0.0742 | [1] | 13% |
| - include empagliflozin treatment effect | | 0.0766 | [1] | 10% |
| - include empagliflozin treatment effect; KM data used over 30 months; extrapolated using a Weibull function | | 0.0670 | [2] | 22% |
| **Heart failure hospitalisation costs (base case $8,674 per event)** | | | | |
| - increase by 50% | [redacted] | 0.0882 | [1] | -15% |
| - decrease by 50% | | 0.0882 | [1] | 15% |
| **CV death costs (base case $9,732 applied to all CV deaths)** | | | | |
| - CV death costs applied to 50% of CV deaths | [redacted] | 0.0882 | [1] | 4% |
| - No CV death costs | | 0.0882 | [1] | 8% |
| **Health state utilities (base case estimates from EMPEROR-Preserved, with general population utility correction)** | | | | |
| - EMPEROR-Preserved estimates, no general population correction | [redacted] | 0.0982 | [1] | -10% |
| **Heart failure hospitalisation QALY loss (base case 0.3354)** | | | | |
| - alternative estimate (QALY loss 0.0279) | [redacted] | 0.0680 | [2] | 30% |
| - 50% reduction (QALY loss 0.1677) | | 0.0772 | [1] | 14% |
| - 75% reduction (QALY loss 0.0838) | | 0.0717 | [2] | 23% |

Source: Table 3.30, pp236-237 of the submission; 'Att_8_Jardiance (empagliflozin) – HF with LVEF more than 40 - CEA' spreadsheet provided with the submission

Abbreviations: CV, cardiovascular; ICER, incremental cost-effectiveness ratio; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; NYHA, New York Heart Association; QALY, quality adjusted life year

[a] Calculated during the evaluation based on 541 events in 2,991 placebo patients and 407 events in 2,997 empagliflozin over an average duration of follow-up of 25.6 months.

*The redacted values correspond to the following ranges*

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

[2] *$25,000 to < $35,000*

[3] *$55,000 to < $75,000*

6.53 The impact of no survival benefit associated with empagliflozin treatment (consistent with clinical evidence) could not be adequately tested during the evaluation. This was due to the model structure that was based on KCCQ-CSS health states with mortality estimates derived from separately modelled survival curves. The ESC considered that the modelled survival benefit was uncertain and therefore a sensitivity analysis was required to assess the impact of the assumed benefit, which was not possible in the

model provided. In the absence of evidence of a survival benefit, the ESC considered that the modelled survival benefit for empagliflozin should be removed from the base in the model. Additional validation would be informative, especially in regard to the relationship between KCCQ-CSS quartiles and cardiovascular death in the proposed population, noting that evidence from the HFrEF population was not relevant.

6.54 The results were most sensitive to the heart failure hospitalisation rate, differences between treatment arms in KCCQ-CSS health state transitions, the QALY loss associated with heart failure hospitalisation, and heart failure hospitalisation costs.

6.55 Regarding cardiovascular mortality, the Pre-PBAC response stated that traces for the cumulative incidence of adjudicated CV death show a clear separation between the empagliflozin and placebo groups from as early as day 720 and continues to widen to the point of data cut-off (see paragraph 6.17). The Pre-PBAC response stated these results are supported by a recently published meta-analysis that pooled data from EMPEROR-Preserved and DELIVER (see paragraph 6.18). The PBAC considered that the meta-analysis published by Vaduganathan et al. (2022) suggested that a modelled mortality benefit was plausible.

## *Drug cost/patient/year*

6.56 The empagliflozin drug cost per patient per year is $732.45, based on the proposed DPMQ per script of $60.16 (updated to incorporate mark-ups from 1 July 2022) / 30 days per script × 365.25 days per year, assuming 100% adherence. 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.

6.57 The economic analysis included estimates of the costs of standard care ($699.96 per year, based on $58.33 per month × 12 months per year), applied to both arms of the model. These costs were not included in the financial estimates.

**Table 13: Drug cost per patient per year for empagliflozin**

| | EMPEROR-Preserved trial | Economic model | Financial estimates |
|---|---|---|---|
| Daily dose | 10 mg daily | 10 mg daily | 10 mg daily |
| Cost per pack of 30 tablets (proposed DPMQ) | - | $60.16[a] | $60.16[a] |
| Adherence | 94.96%[b] | 100% | 94.96%[b] |
| Number of scripts per year | - | 12.175 (=365.25/30 × 100%) | 11.56 (=365.25/30 × 94.96%) |
| Cost per year | - | $732.45 | $695.53 |
| Proportion of patients on treatment (persistence) | At a median follow-up of 26 months, 68.5% of patients in the empagliflozin arm remained on treatment. | Year 1: 85.5%[c]<br>Year 2: 73.7%<br>Year 3: 63.7%<br>Year 4: 54.2%<br>Year 5: 45.5%<br>Year 6: 37.6% | Not explicitly included in the prevalence approach |

Source: Sections 2.3 and 2.4 of the submission; 'Att_8_Jardiance (empagliflozin) – HF with LVEF more than 40 - CEA' and 'Att_11_Jardiance (empagliflozin) – HF with LVEF more than 40 - UCM' spreadsheets provided with the submission

[a] The DPMQ for empagliflozin has been updated to account for July 2022 changes in PBS fees and mark-ups

[b] Based on a post hoc analysis presented in Attachment 4 of the submission. Overall adherence with study medication in both placebo and empagliflozin arms
[c] Estimates based on the proportion of surviving patients on treatment

## *Estimated PBS usage & financial implications*

6.58 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the utilisation and financial impact of listing empagliflozin on the PBS/RPBS for the treatment of heart failure with mildly reduced or preserved ejection fraction.

6.59 Key inputs for the financial estimates are summarised in Table 14.

**Table 14: Key inputs for financial estimates**

| Parameter | Value applied and source | Comment |
|---|---|---|
| HF prevalence | 2,199 per 100,000 adults. Based on the age-adjusted prevalence of definite or probable heart failure from a retrospective review of medical records from Australian general practices (SHAPE study). Previously used in the dapagliflozin and empagliflozin HFrEF submissions. | The publication noted that the prevalence of heart failure may have been underestimated given the difficulty in identifying HFpEF patients as this condition is not as well recognised and does not have any disease-specific therapies. |
| Proportion with LVEF > 40% | 43%. Complement of the assumption previously used to estimate the proportion of patients with LVEF < 40 in the dapagliflozin and empagliflozin HFrEF submissions. | The assumption used in the submission is inconsistent with available Australian epidemiology data (estimates ranging between 52%-59%) and may underestimate the proportion of patients with HFmrEF and HFpEF. In the PSCR the sponsor stated a willingness to accept a higher proportion that is reflective of the Australian studies, should PBAC consider it appropriate. The pre-PBAC response proposed 55%. |
| Proportion with NYHA II-IV | 95%. Assumption used in the sacubitril with valsartan, dapagliflozin and empagliflozin HFrEF submissions. | The assumption was previously implemented in order to address DUSC concerns that the proportion of patients with NYHA I reported in the published literature for the broader heart failure population may be lower in patients with HFrEF (para 6.14; sacubitril with valsartan PSD July 2016 PBAC meeting). As a consequence, the assumption that only 5% of patients have NYHA I is unlikely to be appropriate for HFmrEF and HFpEF populations. |
| Proportion not using SGLT2 inhibitors for other indications | 90.22%. Based on a sponsor-commissioned analysis of the 10% PBS sample assessing the proportion of patients being co-administered heart failure drugs and SGLT2 inhibitors between 2014-2020, with results extrapolated to 2021. | It is unclear whether the subset of patients identified as using heart failure drugs in the analysis is representative of the broader heart failure population or the target population with HFmrEF and HFpEF.<br><br>There was inadequate information on the time periods used to define co-administration and treatment persistence. Additionally, no sensitivity analyses were presented to assess the robustness of rules and definitions used in the dataset.<br><br>It was unclear why the proportion of patients using SGLT2 inhibitors was assumed to remain fixed at 2021 levels. Based on the presented analysis, the coadministration of heart failure drugs and SGLT2 inhibitors has been steadily growing over time and may further increase in the future with |

| Parameter | Value applied and source | Comment |
|---|---|---|
| | | recent changes in diabetes guidelines and the PBAC recommendation of dapagliflozin for chronic kidney disease (March 2022).<br><br>The reported proportion of patients using SGLT2 inhibitors (9.78%) was lower than previous estimates for the broader heart failure population in the empagliflozin (10.6-13.5% with further additional inflation factors) and dapagliflozin (20%) submissions. The PBAC considered that the use of SGLT2 inhibitors is rapidly increasing in other indications.<br><br>The pre-PBAC response reduced this to 80%. |
| Empagliflozin uptake rate | 10-95%. Assumption based on high clinical need and the lack of approved therapies for patients with HFmrEF and HFpEF. | While it may be reasonable to assume high uptake in the target population, the estimates used in the submission appeared implausibly high. These treatment rates are substantially higher than observed for any other treatment in the broader heart failure population (Sindone 2021). Additionally, patients with HFmrEF and HFpEF are typically older with multiple comorbidities and the addition of another therapy would likely be considered on a case-by-case basis given their current treatment burden and fragility. The ESC considered uptake in the early years may be higher than forecast, however agreed with the evaluation that it was implausibly high in Year 4 onwards. The pre-PBAC response proposed different uptake rates between 20-80%. |
| Empagliflozin 10 mg scripts | 11.56/patient/year. Calculated based on an estimated treatment adherence of 94.96% derived from the EMPEROR-Preserved trial | Treatment adherence rates from the EMPEROR-Preserved trial, observed in a tightly regulated setting, are likely to overestimate treatment adherence in the broader clinical setting, especially considering the patient population. The pre-PBAC response proposed 90% compliance. |

Source: Table 4.1, pp239-240 of the submission

Abbreviations: HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PBS, Pharmaceutical Benefits Scheme; SGLT2, sodium-glucose cotransporter-2

6.60 Table 15 presents the estimated use and financial impact of empagliflozin to the PBS/RPBS.

**Table 15: Estimated use and financial implications**

| | Year 1 (2023) | Year 2 (2024) | Year 3 (2025) | Year 4 (2026) | Year 5 (2027) | Year 6 (2028) |
|---|---|---|---|---|---|---|
| Adult Australian population | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] |
| HF prevalence (2,199 per 100,000 adults) | [redacted][2] | [redacted][2] | [redacted][2] | [redacted][2] | [redacted][2] | [redacted][2] |
| Proportion with LVEF > 40% (43%) | [redacted][3] | [redacted][9] | [redacted][9] | [redacted][9] | [redacted][9] | [redacted][9] |
| Proportion with NYHA II-IV (95%) | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][9] | [redacted][9] |
| Proportion not using SGLT2 inhibitors for other indications (90%) | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] |
| Uptake | [redacted]% | [redacted]% | [redacted]% | [redacted]% | [redacted]% | [redacted]% |
| Patients treated with empagliflozin | [redacted][4] | [redacted][10] | [redacted][13] | [redacted][3] | [redacted][3] | [redacted][3] |
| Empagliflozin 10 mg scripts (11.56/patient/year) | [redacted][3] | [redacted][11] | [redacted][7] | [redacted][7] | [redacted][7] | [redacted][7] |
| Cost to PBS/RPBS (DPMQ $60.10) | [redacted][5] | [redacted][12] | [redacted][14] | [redacted][17] | [redacted][19] | [redacted][19] |
| Patient copayment ($[redacted] per script) | [redacted][6] | [redacted][6] | [redacted][6] | [redacted][6] | [redacted][6] | [redacted][6] |
| **Net cost to PBS/RPBS** | [redacted][7] | [redacted][8] | [redacted][15] | [redacted][18] | [redacted][20] | [redacted][19] |
| **Revised inputs for financial estimates and proposed risk share – Pre-PBAC response** | | | | | | |
| Cost to PBS/RPBS less co-payments | [redacted][8] | [redacted][12] | [redacted][16] | [redacted][14] | [redacted][18] | [redacted][20] |

Source: Table 4.8, p244; Table 4.9, p245; Table 4.10, p245; Table 4.11, p245; Table 4.12, p246; Table 4.13, p246 of the submission
Abbreviations: DPMQ, dispensed price per maximum quantity; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme
Note: Costs were calculated using a DPMQ of $60.10, based on mark-ups at 1 June 2022; markups were updated on 1 July 2022, resulting in a new DPMQ of $60.16.
*The redacted values correspond to the following ranges:*
[1] *> 10,000,000*
[2] *400,000 to < 500,000*
[3] *100,000 to < 200,000*
[4] *10,000 to < 20,000*
[5] *$10 million to <$20 million*
[6] *Net cost saving*
[7] *$0 to <$10 million*
[8] *$20 million to <$30 million*
[9] *200,000 to < 300,000*
[10] *40,000 to < 50,000*
[11] *500,000 to < 600,000*
[12] *$30 million to < $40 million*
[13] *80,000 to < 90,000*
[14] *$60 million to < $70 million*
[15] *$50 million to < $60 million*
[16] *$40 million to < $50 million*
[17] *$80 million to < $90 million*
[18] *$70 million to < $80 million*
[19] *$100 million to < $200 million*
[20] *$90 million to < $100 million*

6.61 The estimated net cost to the PBS/RPBS for empagliflozin was $10 million to < $20 million in Year 1, increasing to $100 million to < $200 million in Year 6, with a

cumulative total of $300 million to < $400 million over the first 6 years of listing. The Pre-PBAC response provided revised financial estimates and proposed a risk sharing arrangement based on these estimates with a cumulative total of $300 million to < $400 million over the first 6 years of listing (see Table 15). Heart failure with mildly reduced or preserved ejection fraction appears to be a relatively common but under-recognised condition in older populations. Overall, there are limited data to reliably inform Australian estimates of prevalence and functional status.

6.62 In regard to the proportion of patients with LVEF > 40%, the PSCR stated that a conservative estimate of 43% was used in the submission as this represents the complement of the proportion of patients with LVEF ≤40% which was accepted by the PBAC during its evaluation of dapagliflozin (Dapagliflozin PSD, September 2021). The PSCR agreed with the Commentary that this could be an underestimation as Australian epidemiological studies have reported a higher proportion ranging from 52% to 59% (see Table 14).

6.63 The estimation of the proportion of patients already using SGLT2 inhibitors for other indications (diabetes, heart failure) was based on an analysis of the 10% PBS sample which may not be applicable to the target population, was poorly documented and included an unrealistic assumption of fixed utilisation over time (particularly given the March 2022 PBAC recommendation to extend the dapagliflozin listing to include chronic kidney disease).

6.64 The proposed uptake (up to 95% in the 6th year) and treatment adherence (94.96%) estimates for empagliflozin use in the target population appear to be implausibly high and are unlikely to be reflective of clinical practice. The ESC noted that HFpEF/HFmrEF is a common condition and considered there was significant financial uncertainty associated with the proposed PBS listing as summarised below. The ESC considered the population has a very high unmet need, and that uptake of empagliflozin may be rapid after PBS listing.

6.65 The ESC considered the estimated use and financial implications to the RPBS/PBS of listing empagliflozin were uncertain for the following reasons:

- The prevalence may have been underestimated given the difficulty in identifying HFpEF patients as this condition is not as well recognised compared with HFrEF (see Table 14).
- Assumption used on the proportion of HF patients with LVEF>40% is inconsistent with available Australian epidemiology data (submission used 43%, other estimates ranging between 52%-59%; see Table 14). The pre-PBAC response revised this estimate from 43% to 55%, which was the midpoint of estimates from Australian epidemiology data (52% to 59%).
- The risk of empagliflozin use outside the requested restriction is high (see paragraph 6.68).

- Submission's estimate of the proportion using SGLT2 inhibitors (9.78%) was lower than previous estimates used in previous empagliflozin (10.6-13.5% with further additional inflation factors) and dapagliflozin (20%) submissions (see Table 14, and paragraph 6.63). The pre-PBAC response revised this estimate to 20%, which was consistent with the estimate assumed in the dapagliflozin submission for HFrEF.
- Peak uptake rates and treatment adherence (95%) appear very high (see paragraph 6.64). The ESC considered a more reasonable span for uptake rates would be from 20% in Year 1 to 70% in year 6. The pre-PBAC response proposed revised uptake over 6 years between 20-80%. The higher uptake rate towards Year 6 was proposed based on the likely availability of additional SGLT2 inhibitors and limited access to new treatments in this patient population.

## *Quality Use of Medicines*

6.66 The submission identified a number of potential quality use of medicines issues including:

- The use of inappropriate dose strengths: empagliflozin is currently listed for diabetes with two dose strengths (10 and 25 mg) while only one dose strength is proposed for heart failure (10 mg).
- Inadvertent co-prescribing of empagliflozin with other SGLT2 inhibitors used for the treatment of diabetes.
- Confusion about dosing in renal impairment given the different proposed eGFR cutoffs for diabetes (30mL/min/1.73 $m^2$) and heart failure (20mL/min/1.73 $m^2$).
- The management of adverse events.

6.67 To address these concerns, the submission proposed a series of quality use of medicine initiatives including face-to-face interactions, digital content and print materials for patients and healthcare professionals to ensure appropriate use of empagliflozin in heart failure patients with mildly reduced or preserved ejection fraction.

## *Financial Management – Risk Sharing Arrangements*

6.68 The ESC considered there was substantial risk of usage in patients with unexplained breathlessness without HFmrEF/HFpEF and due to other causes, including age, body habitus, respiratory disease, physical deconditioning etc.

6.69 The Pre-PBAC response proposed a risk sharing arrangement as shown in Table 15), a rebate of 50% above the caps was proposed.

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

# 7 PBAC Outcome

7.1 The PBAC did not recommended empagliflozin for the treatment of chronic heart failure in patients with a left ventricular ejection fraction greater than 40%. The PBAC considered there was a high unmet clinical need for effective treatments for patients with this condition. The PBAC noted that empagliflozin when added to standard care provided a statistically significant improvement in efficacy over standard care alone in the proposed population. However, the reduction in hospitalisations due to heart failure were modest and there remained considerable uncertainty in the extent of any mortality benefit. The PBAC noted the economic model did not adequately capture the progressive nature of the disease. The PBAC considered that a price reduction to achieve a lower incremental cost-effectiveness ratio (ICER) was required to reflect the moderate clinical benefits shown in the clinical evidence and the uncertain extrapolated benefit. The PBAC considered that a risk sharing arrangement would be required due to a high risk of utilisation outside the proposed restriction.

7.2 The PBAC welcomed the expert advice from the sponsor hearing and agreed that there was an unmet need for effective treatments in chronic heart failure with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF).

7.3 The PBAC accepted the nominated comparator of standard care was appropriate, noting that dapagliflozin may be a near market comparator with the recent publication of the DELIVER trial[4] and TGA regulation dossier[5].

7.4 The PBAC noted that the submission was based on one head-to-head randomised trial (n=5,998) comparing empagliflozin plus standard care versus placebo plus standard care in patients with (HFmrEF/HFpEF) (EMPEROR-Preserved). Treatment with empagliflozin was associated with a statistically significant improvement in the primary composite endpoint of time to cardiovascular death, or hospitalisation for heart failure compared to placebo (hazard ratio: 0.79; 95% CI 0.69, 0.90), over a median duration of follow-up of 26 months. The PBAC noted that the absolute risk reduction in the primary composite endpoint (3.2% over a median follow-up of 26 months) was lower than for the HFrEF population for empagliflozin in EMPEROR-Reduced (5.3% over a median duration of follow-up of 16 months, see paragraph 6.11). The PBAC considered this reflected a more modest treatment effect for empagliflozin in the HFmrEF/HFpEF population compared with the HFrEF population.

7.5 The PBAC noted that efficacy of empagliflozin had been demonstrated over pooled LVEF subgroups in EMPEROR-Reduced and EMPEROR-Preserved (Table 7).The PBAC

[4] Solomon SD et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med. 2022 Sep 22;387(12):1089-1098. doi: 10.1056/NEJMoa2206286. Epub 2022 Aug 27.
[5] https://www.tga.gov.au/resources/prescription-medicines-under-evaluation/forxiga-astrazeneca-pty-ltd

considered that the LVEF ≥ 65% subgroup was likely a very heterogenous population, including many patients who did not have HFpEF, which was consistent with the conclusions of the study authors (see paragraph 6.25).

7.6 The PBAC noted the underlying event rate differed for the HFmrEF/HFpEF population compared with the HFrEF population, for example the event rate for CV death in the EMPEROR-Preserved trial (3.8 per 100 patient years in the placebo arm of the trial) was much lower than that in the EMPEROR-Reduced trial (8.1 per 100 patient years, see paragraph 6.17). Although these event rates contributed to the uncertain extent of benefit in a reduction in CV mortality, the PBAC noted the meta-analysis of the dapagliflozin and empagliflozin trials showed that SGLT2 inhibitors reduced CV mortality by 12% with nominal significance (see paragraph 6.18). Coupled with the clinically meaningful improvements in KCCQ clinical summary scores (see paragraph 6.20), the PBAC considered that some CV mortality benefit could plausibly be expected.

7.7 The PBAC considered that the safety profile of empagliflozin is well understood due to its use in other indications, and the results from the EMPEROR-Preserved trial were consistent with the known safety profile of empagliflozin in the treatment of type 2 diabetes and HFrEF, with no unexpected safety signals detected. The PBAC noted that the proportion of patients experiencing adverse events was similar for the empagliflozin and placebo groups (85.9% vs 86.5%, respectively) and the claim of non-inferior comparative safety to standard care was accepted.

7.8 The submission presented a cost-utility analysis of empagliflozin plus standard care versus standard care alone, in patients with HFmrEF/HFpEF based on the results of the EMPEROR-Preserved trial. The PBAC noted that the health states were defined based on KCCQ-CSS quartiles and considered that KCCQ score was a validated and accepted measure in this population, but that multiple inputs and assumptions in the economic model were inconsistent with disease progression. In particular it was noted:

- hospitalisation for heart failure was included as a transient event 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 model does not account for mortality impacts associated with re-admissions to hospital, as well as declining utility and increases in ongoing costs.
- constant transition probabilities between KCCQ-CSS quartile health states from 9 months to the end of the 15 year model time horizon were derived from individual patient data from the EMPEROR-Preserved trial over the 9-12 month period. This did not adequately reflect longer term health outcomes in a progressive disease.

7.9 Based on the modelled economic evaluation, treatment with empagliflozin plus standard care was associated with an ICER of $15,000 to < $25,000 per QALY gained compared to standard care alone for the treatment of HFmrEF/HFpEF. The PBAC considered that a lower ICER was required to reflect the model uncertainty and the

modest clinical benefits shown in the clinical evidence. The PBAC advised that use of the submission model and inputs would be appropriate in a resubmission if the price was reduced to correspond to an ICER of less than $15,000 to < $25,000 per QALY gained.

7.10 The PBAC considered that HFmrEF/HFpEF is a relatively common but often under-recognised condition in older populations. The PBAC considered there is a substantial risk of leakage of empagliflozin to populations with dyspnoea of multifactorial aetiology and which may not exclusively or predominantly be due to HFpEF, resulting in use in populations where cost-effectiveness has not been demonstrated and creating considerable financial uncertainty. The PBAC noted that the pre-PBAC response had presented revised financial estimates, which acknowledged the concerns raised by the ESC. The PBAC considered that the adjustments applied in the revised estimates were reasonable (see paragraph 6.65).

7.11 The PBAC considered that a risk sharing arrangement would be required due to a high risk of utilisation outside the proposed restriction. The PBAC considered that a rebate of 100% above the caps would be appropriate. The PBAC noted that risk sharing arrangements are in place for empagliflozin in its HFrEF indication currently. The PBAC considered a separate cap would be appropriate for the proposed HFmrEF/HFpEF listing due to the substantial risk of leakage for this indication as described in paragraph 7.10.

7.12 The PBAC considered the outstanding issues may be addressed in a simple resubmission for empagliflozin using the early re-entry pathway. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation.

- Use of the current submission economic model with a price reduction to achieve an ICER of less than $15,000 to < $25,000 per QALY gained.
- Revised financial estimates using the inputs from the pre-PBAC response and recalculation of the financial implications using the revised empagliflozin price.
- A risk sharing arrangement with a 100% rebate above the caps, based on the revised financial estimates.

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

7.14 With regard to the restriction, the PBAC noted that one of the proposed diagnostic tests (NT-proBNP testing) is not routinely used in Australian clinical practice. The PBAC considered that the criterion in relation to NT-proBNP testing should be retained as one of the options for determination of eligibility for empagliflozin, however it should

only apply for patients with elevated NT-proBNP levels "in the absence of another cause". The PBAC emphasised that patients would not need to seek NT-proBNP testing to access reimbursed empagliflozin treatment but that a small number of patients may have these results available if levels have previously been tested. The PBAC agreed with the ESC's recommended revision to the proposed restriction to reflect that the requirement for documented evidence of structural changes in the heart on echocardiography would apply for all patients, in addition to at least one of four additional criteria, including NT-proBNP criterion (see paragraph 3.7).

7.15 The PBAC also agreed with the ESC that it was appropriate not to require concomitant use with optimal standard chronic heart failure treatment including a beta-blocker and an ACEi/ARB/ARNi (which currently applies in the restriction for patients with LVEF ≤40%), given there is a lack of evidence for specific disease-modifying therapies for heart failure patients with preserved ejection fraction (see paragraph 3.5).

7.16 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**
Not recommended

# 8 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.

# 9 Sponsor's Comment

The sponsor had no comment.

**Addendum to the November 2022 PBAC PSD:**

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

## 10 Background

10.1 At the November 2022 meeting, the PBAC did not recommend empagliflozin for the treatment of chronic heart failure in patients with a left ventricular ejection fraction (LVEF) greater than 40%. The PBAC considered that the outstanding issues could be addressed in a simple resubmission using the early re-entry pathway if the matters outlined in Table 1 were addressed.

10.2 Following the November 2022 meeting, the sponsor submitted a letter for PBAC consideration on 16 December 2022. A summary of the issues addressed in that letter is also outlined in Table 1.

**Table 1: Issues to be addressed (November 2022 PBAC PSD)**

| Matter of Concern | | Letter from sponsor (16 December 2022) |
|---|---|---|
| **Matters Raised by PBAC (PSD, para 7.12)** | | |
| 1 | Use of the current submission economic model with a price reduction to achieve an ICER of less than $[redacted][1] per QALY gained.<br><br>An ICER of $[redacted][1]/QALY gained corresponds to AEMP = $[redacted] for empagliflozin, reflecting [redacted]% reduction from submission price (AEMP=$44.66). | The sponsor proposed a reduced price for empagliflozin, AEMP= $[redacted], reflecting a [redacted]% reduction. The corresponding ICER is $[redacted][1]/QALY. |
| 2 | Revised financial estimates using the inputs from the pre-PBAC response and recalculation of the financial implications using the revised empagliflozin price. | The sponsor provided revised estimates, see Table 2. |
| 3 | A risk sharing arrangement with a 100% rebate above the caps, based on the revised financial estimates. | The letter stated that the sponsor will accept a risk sharing arrangement with [redacted] rebate above agreed caps. |
| **Additional matters raised by Sponsor** | | |
| 4 | Restriction wording | The sponsor requests the PBAC consider revised restriction wording – see below. |
| 5 | Special Pricing Arrangement | The sponsor requests a special pricing arrangement |

Source: Empagliflozin, PBAC Public Summary Document (PSD), November 2022 PBAC meeting; Letter from Boehringer Ingelheim, 16 December 2022.

*The redacted values correspond to the following ranges*
[1]$15,000 to < $25,000

10.3 Revised financial estimates using the inputs from the November 2022 pre-PBAC response and recalculation of the financial implications using the revised empagliflozin price from the 16 December 2022 letter are presented in Table 2. A risk sharing

arrangement with [redacted] rebate above the revised caps in Table 2 was also accepted by the sponsor.

**Table 2: Revised estimated use and financial implications**

| | Year 1 (2023) | Year 2 (2024) | Year 3 (2025) | Year 4 (2026) | Year 5 (2027) | Year 6 (2028) | Y1-Y6 |
|---|---|---|---|---|---|---|---|
| **Current estimates (Letter dated 16 Dec 2022)** | | | | | | | |
| Net cost PBS / RPBS (Effective AEMP=$[redacted]) | $[redacted][1] | $[redacted][2] | $[redacted][3] | $[redacted][4] | $[redacted][5] | $[redacted][6] | $[redacted][7] |
| Proposed rebate above caps | [redacted] | | | | | | |
| **November 2022 Pre-PBAC response** | | | | | | | |
| Net cost PBS / RPBS (Effective AEMP=$44.66) | $[redacted][2] | $[redacted][3] | $[redacted][4] | $[redacted][8] | $[redacted][6] | $[redacted][9] | $[redacted][10] |

Source: Empagliflozin, PBAC Public Summary Document, November 2022; Letter from Boehringer Ingelheim, 16 December 2022.

*The redacted values correspond to the following ranges:*
*[1]$10 million to < $20 million*
*[2]$20 million to < $30 million*
*[3]$30 million to < $40 million*
*[4]$40 million to < $50 million*
*[5]$50 million to < $60 million*
*[6]$70 million to < $80 million*
*[7]$200 million to < $300 million*
*[8]$60 million to < $70 million*
*[9]$90 million to < $100 million*
*[10]$300 million to < $400 million*

# 11 Other considerations

## *Requested restriction*

11.1 In November 2022, the PBAC recommended revision to the proposed restriction to reflect that the requirement for documented evidence of structural changes in the heart on echocardiography would apply for all patients, in addition to at least one of four additional criteria, including NT-proBNP criterion (see paragraphs 3.7 and 7.14 above).

11.2 The sponsor letter from 16 December 2022 highlighted a concern that this requirement would exclude a small subset of patients who (a) may not have overt structural changes on echocardiography but have evidence of diastolic dysfunction such as high filling pressure that would be diagnostic of heart failure, or (b) have no or poorly documented echocardiography results from prior hospitalisation for heart failure event.

11.3 The letter requested the PBAC accept the Secretariat revised wording from the November 2022 submission (see proposed wording under paragraph 3.1 above) or alternatively a further revision to the wording be made to more closely reflect current Australian clinical guidelines (see Figure 1 below).

**Figure 1: Proposed alternative wording for the clinical criteria for the restriction**

**Table 2 Proposed alternative wording for the clinical criteria for the restriction**

| | Clinical criteria: |
|---|---|
| New CC2 | Patient must have documented evidence of hospitalisation for heart failure within the 12 months prior to initiating treatment with this drug<br>**OR**<br>Patient must have documented echocardiography within the 12 months prior to initiating treatment with this drug<br>**AND**<br>Patient must have documented evidence of at least one of:<br>(i) structural changes in the heart on echocardiography that would be expected to cause diastolic dysfunction (e.g. left ventricular hypertrophy); **OR**<br>(ii) diastolic dysfunction with high filling pressure on echocardiography, stress echocardiography or cardiac catheterisation; **OR**<br>(iii) requirement for intravenous diuretic therapy in the 12 months prior to initiating treatment with this drug **OR**<br>(iv) elevated N-terminal pro brain natriuretic peptide (NT-proBNP) levels in the absence of another cause |

Source: letter from Boehringer Ingelheim, 16 December 2022.

# 12 PBAC Outcome

12.1 The PBAC recommended extending the existing listing of empagliflozin to include a General Schedule Authority Required (Streamlined) listing for the treatment of chronic heart failure in patients with a left ventricular ejection fraction greater than 40%. The PBAC considered there was a high unmet clinical need for effective treatments for patients with this condition. The PBAC noted that empagliflozin when added to standard care provided a statistically significant improvement in efficacy over standard care alone in the proposed population based on the primary composite outcome in EMPEROR-Preserved (time to first cardiovascular death or hospitalisation for heart failure). The PBAC considered that the sponsor had addressed the substantive outstanding issues identified at the November 2022 PBAC meeting via the proposed price reduction and risk sharing arrangement. The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of empagliflozin would be acceptable at the price proposed in the revised offer of 16 December 2022.

12.2 The PBAC noted the revised price offered was [redacted]% below the current price for chronic heart failure in patients with LVEF ≤40% and resulted in an ICER of $15,000 to < $25,000/QALY gained for patients with chronic heart failure in patients with LVEF >40%. This price reduction was deemed acceptable in reference to the issues raised in section 7 regarding a more modest treatment effect in patients with chronic heart failure with preserved or mildly reduced ejection fraction (HFpEF or HFmrEF) compared to those with chronic heart failure with reduced ejection fraction (HRrF), and the model uncertainty.

12.3 The PBAC noted the proposed RSA now included a [redacted] rebate over the revised caps, which aligned with the November 2022 PBAC advice. The PBAC recalled that in November 2022, it had considered a separate cap would be appropriate for the proposed HFmrEF/HFpEF listing due to the substantial risk of leakage for this indication into populations with dyspnoea of multifactorial aetiology and which may not exclusively or predominantly be due to HFpEF (see paragraph 7.11).

12.4 The PBAC noted the request for modification of the proposed restriction criteria, however considered that the criteria were appropriate as documented in the November 2022 PBAC PSD (paragraph 3.7 and 7.14). The PBAC advised the wording was chosen to ensure that patients who do not have HFpEF do not receive it, rather than inadvertently excluding people who do have HFpEF. The PBAC disagreed with the sponsor that the population who does not have structural changes would be a "small but vulnerable patient population" and that access to echocardiography should pose a block to access to the drug. A cardiac reason for HFpEF (left ventricular hypertrophy (LVH), valvular disease etc) is a necessary prerequisite for access otherwise patients with symptoms, but who have multiple other (potential) causes of dyspnoea (age, physical fitness, body mass index (BMI) etc) can be diagnosed with HFpEF. The PBAC considered that all patients treated with empagliflozin for HFpEF should have had an echocardiogram at least in the last 12 months. Thus, the PBAC considered the approaches proffered by the sponsor are not going to be sufficiently targeted, and the PBAC requirement that evidence of structural change is a necessary but insufficient criteria (i.e. cannot be an OR but must be an AND) should remain.

12.5 The PBAC considered that a further clinician meeting could be held to discuss any residual concerns about the proposed restriction criteria if required.

12.6 The PBAC advised that empagliflozin is suitable for prescribing by nurse practitioners within collaborative arrangements as continuing therapy only. This would be consistent with existing arrangements for empagliflozin for LVEF ≤40%.

12.7 The PBAC recommended that the Early Supply Rule should apply to the proposed listing, which would be consistent with the current PBS listings for empagliflozin.

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

i) The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy, over alternative therapies, on the basis that the treatment effect in the proposed PBS population is modest with uncertainty as to the degree of substantial and clinically relevant improvement in efficacy, over alternative therapies.

ii) The treatment is expected to address a high and urgent unmet clinical need

because there are currently no effective treatments for patients with HFmrEF/HFpEF.

iii) 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.

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

**Outcome:**
Recommended

# 13 Recommended listing

13.1 Add new item:

| **MEDICINAL PRODUCT medicinal product pack** | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№.of Rpts** | **Available brands** |
|---|---|---|---|---|---|
| EMPAGLIFLOZIN | | | | | |
| empagliflozin 10 mg tablet, 30 | NEW | 1 | 30 | 5 | Jardiance |
| | | | | | |
| **Restriction Summary / Treatment of Concept:** | | | | | |
| **Category / Program:** GENERAL – General Schedule (Code GE) | | | | | |
| **Prescriber type:** ☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives | | | | | |
| **Restriction type:** ☒Authority Required (Streamlined) | | | | | |
| **Administrative Advice:**<br>**Continuing Therapy Only:**<br>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.* | | | | | |
| **Indication:** Chronic heart failure | | | | | |
| **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 greater than 40% | | | | | |
| **AND** | | | | | |
| **Clinical criteria:** | | | | | |

| |
|---|
| ~~Patient must have documented evidence of *at least one of:*~~<br>~~*(i) relevant* structural changes in the heart on echocardiography; OR~~<br>~~(ii) diastolic dysfunction with high filling pressure on echocardiography; OR~~<br>~~(iii) hospitalisation *due to* heart failure; OR~~<br>~~(iv) elevated N-terminal pro brain natriuretic peptide (NT-proBNP) level s~~<br><br>*Patient must have documented evidence of:*<br>*Structural changes in the heart on echocardiography that would be expected to cause diastolic dysfunction (e.g. left ventricular hypertrophy); AND*<br>*At least one of*<br>*(i) diastolic dysfunction with high filling pressure on echocardiography, stress echocardiography or cardiac catheterisation; OR*<br>*(ii) hospitalisation for heart failure in the 12 months prior to initiating treatment with this drug OR*<br>*(iii) requirement for intravenous diuretic therapy in the 12 months prior to initiating treatment with this drug OR*<br>*(iv) elevated N-terminal pro brain natriuretic peptide (NT-proBNP) levels in the absence of another cause* |
| **AND** |
| **Clinical criteria:** |
| Patient must not be receiving treatment with another sodium-glucose co-transporter 2 (SGLT2) inhibitor. |

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

# 14 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.

# 15 Sponsor's Comment

The sponsor had no comment.