

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

### 1 Purpose of submission

- 1.1 The Category 2 submission requested an Authority Required (Streamlined) listing of empagliflozin for the treatment of patients with chronic heart failure with reduced ejection fraction (HFrEF), New York Heart Association classification II-IV, left ventricular ejection fraction (LVEF)  $\leq 40\%$ , receiving standard care including a beta blocker, and an angiotensin-converting enzyme inhibitor (ACEi), or an angiotensin II receptor blocker (ARB), or an angiotensin receptor with neprilysin inhibitor (ARNi).
- 1.2 Listing was requested on the basis of a cost-utility analysis for empagliflozin plus standard care (SC) versus SC alone. The submission also included a clinical claim of noninferiority to dapagliflozin plus SC, which had been recommended for listing by PBAC at its September Intracycle meeting. Therefore, the PBAC considered it appropriate for the listing to be considered on a cost-minimisation basis with dapagliflozin plus SC (see also 'Comparator' section).

**Table 1: Key components of the clinical issue addressed by the submission**

Component	Description
Population	Adult patients (NYHA Class II-IV) with HFrEF defined as LVEF $\leq 40\%$ .
Intervention	Empagliflozin 10 mg once daily in addition to standard care (SC).
Comparator	Placebo in addition to SC, defined as: - an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, in combination with a beta-blocker, $\pm$ a mineralocorticoid receptor antagonist; or - sacubitril/valsartan, in combination with a beta-blocker, $\pm$ a mineralocorticoid receptor antagonist. Dapagliflozin in addition to SC (potential near market comparator).
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 plus SC is superior in terms of effectiveness, and noninferior in terms of safety, compared with placebo plus SC. Empagliflozin plus SC is noninferior in terms of effectiveness and safety compared with dapagliflozin plus SC.

Source: Table 1.1, p2 of the submission.

HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SC, standard care.

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

### 2 Background

#### Registration status

- 2.1 **TGA status at time of PBAC consideration:** The submission was made under the TGA/PBAC parallel process. At the time of evaluation, the Round 1 TGA Clinical

Evaluation Report was available. A positive TGA delegate's overview was available prior to the PBAC meeting.

- 2.2 The indication in the TGA delegate's overview was:
- "JARDIANCE is indicated in adults for the treatment of symptomatic heart failure with reduced 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, and 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.

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

### 3 Requested listing

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
EMPAGLIFLOZIN Tablets 10 mg, (30)	1	30	5	\$60.04	Jardiance®, Boehringer Ingelheim Pty Ltd
Category/Program:	GENERAL – General Schedule (Code GE)				
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives				
PBS indication:	Chronic heart failure				
Restriction:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input type="checkbox"/> Authority Required – Telephone, Electronic <input checked="" type="checkbox"/> Streamlined				
Clinical criteria:	<p>Patient must be symptomatic with NYHA classes II, III or IV, AND</p> <p>Patient must have a documented left ventricular ejection fraction (LVEF) of less than or equal to 40%, AND</p> <p>Patient must receive concomitant optimal standard chronic heart failure treatment, which must include a beta-blocker, unless at least one of the following is present in relation to the beta-blocker (i) a contraindication listed in the Product Information, (ii) an existing/expected intolerance, (iii) local treatment guidelines recommend initiation of this drug product prior to a beta-blocker, AND</p> <p>Patient must be receiving treatment with an ACE inhibitor, unless contraindicated according to the TGA-approved Product Information or cannot be tolerated; OR            Patient must be receiving treatment with an angiotensin II antagonist, unless contraindicated according to the TGA-approved Product Information or cannot be tolerated; OR            Patient must be receiving treatment with an angiotensin receptor with neprilysin inhibitor combination therapy unless contraindicated according to the TGA-approved Product Information or cannot be tolerated.            AND</p> <p>Patient must not be receiving treatment with another sodium-glucose co-transporter 2 (SGLT2) inhibitor.</p>				
Administrative advice:	Continuing Therapy Only: For prescribing by Nurse Practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners				

- 3.1 The requested dispensed price for empagliflozin of \$60.04 (DPMQ per pack of 30 tablets) was the same as the PBS listed price of empagliflozin 10 mg tablets for type 2 diabetes at the time of submission. Following July 2021 changes in fees and mark-ups, the DPMQ for empagliflozin for the treatment of type 2 diabetes was \$60.10.
- 3.2 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).

- 3.3 The requested restriction was narrower than the indication in the TGA delegate’s overview, restricting eligibility to patients with NYHA class II-IV heart failure with a LVEF of  $\leq 40\%$ , receiving concomitant standard chronic heart failure treatment, unless contraindicated or not tolerated.
- 3.4 The requested restriction was broadly consistent with the inclusion criteria of the key clinical trial (EMPEROR-Reduced).
- 3.5 The submission stated that the requested restriction was based on the restriction requested for dapagliflozin (HFrEF), considered by the PBAC at its November 2020 meeting, including the Secretariat suggested wording (para 3.1, dapagliflozin Public Summary Document (PSD), November 2020 PBAC meeting). The only difference in the proposed restriction for empagliflozin was the requirement in relation to beta-blocker use. The submission stated that this was because, on 1 June 2021, the beta-blocker criterion on the sacubitril + valsartan listing was changed from:
  - a. “Patient must receive concomitant optimal standard chronic heart failure treatment, which must include the maximum tolerated dose of a beta-blocker, unless contraindicated or not tolerated.”
  - to
  - b. “Patient must receive concomitant optimal standard chronic heart failure treatment, which must include a beta-blocker, unless at least one of the following is present in relation to the beta-blocker: (i) a contraindication listed in the Product Information, (ii) an existing/expected intolerance, (iii) local treatment guidelines recommend initiation of this drug product prior to a beta-blocker.”
- 3.6 This change to the sacubitril + valsartan listing was in response to a recommendation made in November 2020 when PBAC considered that the previous criterion was “inconsistent with clinical guidelines and may complicate management of patients” (para 7.6, sacubitril + valsartan, PSD, November 2020). The empagliflozin pre-PBAC response considered that there is no consensus regarding a strict sequential approach (i.e. fully titrating one medication class before initiating an additional agent).
- 3.7 The ESC noted that the European Society of Cardiology released its updated *Guidelines for the diagnosis and treatment of acute and chronic heart failure* in August 2021. The revised guidelines note (pp21-22):
  - c. “The triad of an ACE-I/ARNI, a beta-blocker, and an MRA is recommended as cornerstone therapies for these patients, unless the drugs are contraindicated or not tolerated. They should be uptitrated to the doses used in the clinical trials (or to maximally tolerated doses if that is not possible).”

- d. “Unless contraindicated or not tolerated, dapagliflozin or empagliflozin are recommended for all patients with HFrEF already treated with an ACE-I/ARNI, a beta-blocker, and an MRA, regardless of whether they have diabetes or not.”
  - e. That the recommendations for use of an ACE-I, beta-blocker, MRA, and SGLTi are all Class I recommendations, based on Level A evidence.
- 3.8 The PBAC considered that the PBS listing should align with the recommended listing for dapagliflozin.

*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 preserved left ventricular ejection fraction (National Heart Foundation of Australia); i.e. heart failure with reduced ejection fraction (HFrEF: LVEF <40% with clinical symptoms of heart failure and systolic dysfunction); heart failure with preserved ejection fraction (HFpEF: LVEF ≥50% with clinical symptoms of heart failure and objective evidence of structural heart disease and/or diastolic dysfunction; previously defined as diastolic failure); and heart failure with mildly reduced ejection fraction (HFmrEF: LVEF 40-49% with clinical symptoms of heart failure and evidence of diastolic dysfunction).
- 4.3 Liew et al. (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 et al., 2012). Heart failure mortality studies estimate 3- and 4-year survival rates for HFrEF of 32% and 41%, respectively (Somaratne et al., 2009; Meta-analysis Global Group in Chronic Heart Failure, 2012).
- 4.4 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 HFrEF 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.

- 4.5 The proposed clinical management algorithm positioned empagliflozin 10 mg once daily as an add-on to SC in the treatment of chronic HFrEF. This was broadly consistent with the expected TGA indication and the inclusion criteria of the key clinical trial.

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

## **5 Comparator**

- 5.1 The submission nominated optimised SC as the main comparator, comprised of either (i) an ACEi/ARB, in combination with a beta-blocker, with or without an MRA; or (ii) an ARNi, in combination with a beta-blocker, with or without an MRA. This was the comparator used in the key clinical trial (EMPEROR-Reduced), and the appropriate main comparator identified in the November 2020 consideration of dapagliflozin for HFrEF (para 5.6, dapagliflozin, PSD, November 2020 PBAC meeting).

- 5.2 The submission also identified dapagliflozin as a potential near market comparator and pharmacological analogue. The submission acknowledged that if dapagliflozin was listed on the PBS for the treatment of HFrEF, dapagliflozin may be the appropriate main comparator. The PBAC recommended the PBS listing of dapagliflozin for HFrEF at its September 2021 Intracycle meeting. Therefore, dapagliflozin was the appropriate main comparator for this submission.

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician described how SGLT2 inhibitors offered a new mechanism of action and improved effectiveness compared with the existing neurohormonal inhibitors and modulators for heart failure treatment. The clinician also noted recent positive outcomes reported for empagliflozin for the treatment of heart failure with preserved ejection fraction. The clinician highlighted that international consensus is that empagliflozin and dapagliflozin are highly similar drugs, both having Class I recommendations, based on Level A evidence, in the European Society of Cardiology *Guidelines for the diagnosis and treatment of acute and chronic heart failure*. The clinician also noted that the recommendation did not apply to other SGLT2 inhibitors. The clinician further commented on the appropriate noninferiority margin for an indirect treatment comparison (ITC) between empagliflozin and dapagliflozin, supporting the submission's nominated margin of 1.3 as being clinically and scientifically reasonable, and noting that the 1.104 previously considered reasonable by ESC in the context of the dapagliflozin submission for HFrEF was derived from a head-to-head trial with

applicability issues to current practice, and was likely overly stringent for the submission's ITC comparison. The PBAC noted that the hearing aligned with the ESC's advice (see paragraph 6.15).

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from health care professionals (HCP, 2) and the Centre for Community-Driven Research (CCDR) via the Consumer Comments facility on the PBS website. The CCDR survey data (n=50) outlined the impact that having heart failure has on quality of life and relationships. It described patient expectations of future treatment (e.g. wanting less invasive treatments for heart failure, and hoping for treatments that will stabilise or slow disease progression). The comments from HCPs described benefits of treatment with empagliflozin including avoidance of hospitalisation due to heart failure (and associated costs), and improved quality of life. The comments from HCPs also described the challenges with currently available treatments in terms of dosing, adherence, and side effects, and stated that empagliflozin should be available for those patients with HFrEF who are unable to tolerate existing standard of care.

### ***Clinical trials***

- 6.3 The submission was based on one head-to-head randomised trial comparing empagliflozin plus SC versus placebo plus SC (EMPEROR-Reduced), and an ITC of empagliflozin plus SC (EMPEROR-Reduced) versus dapagliflozin plus SC (DAPA-HF), using placebo plus SC as a common reference.
- 6.4 Details of the trials presented in the submission are provided in the table below.

**Table 2: Trials presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Empagliflozin</b>		
EMPEROR-Reduced (Trial 1245-121)	<p>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 reduced Ejection Fraction (HFrEF).</p> <p>Packer M, Anker SD, Butler J et al. Effect of empagliflozin on the clinical stability of patients with heart failure and a reduced ejection fraction: The EMPEROR-Reduced trial.</p> <p>Anker SD, Butler J, Filippatos G, et al. Effect of empagliflozin on cardiovascular and renal outcomes in patients with heart failure by baseline diabetes status - Results from the EMPEROR-Reduced trial.</p> <p>Butler J, Anker SD, Filippatos G, et al. Empagliflozin and health-related quality of life outcomes in patients with heart failure with reduced ejection fraction: the EMPEROR-Reduced trial.</p> <p>Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure.</p> <p>Packer M. Effect of empagliflozin on major heart failure outcomes, renal function and quality of life in patients with heart failure with a reduced ejection fraction, with and without sacubitril/valsartan.</p> <p>Packer M, Anker SD, Butler J, et al. Influence of neprilysin inhibition on the efficacy and safety of empagliflozin in patients with chronic heart failure and a reduced ejection fraction: the EMPEROR-Reduced trial.</p> <p>Zannad F, Ferreira JP, Pocock SJ, et al. Cardiac and kidney benefits of empagliflozin in heart failure across the spectrum of kidney function: insights from the EMPEROR-Reduced trial.</p>	<p>Clinical Study Report, 15 September 2020.</p> <p><i>Circulation</i> 2021, 143(4):326-336.</p> <p><i>Circulation</i> 2021, 143(4):337-349.</p> <p><i>European Heart Journal</i> 2021, 42(13):1-10.</p> <p><i>New England Journal of Medicine</i> 2020, 383(15):1413-1424.</p> <p><i>Journal of Cardiac Failure</i> 2020, 26(12):1109.</p> <p><i>European Heart Journal</i> 2021, 42(6):671-680.</p> <p><i>Circulation</i> 2021, 143(4):310-321.</p>
<b>Dapagliflozin</b>		
DAPA-HF (NCT03036124)	<p>Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF).</p> <p>McMurray JJV, DeMets DL, Inzucchi SE, et al. The Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) trial: baseline characteristics.</p> <p>McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction.</p> <p>McMurray JJV, DeMets DL, Inzucchi SE, et al. A trial to evaluate the effect of the sodium-glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF).</p>	<p>Clinical Study Report, October 2019.</p> <p><i>European Journal of Heart Failure</i> 2019, 21(11):1402-1411.</p> <p><i>New England Journal of Medicine</i> 2019, 381(21): 1995-2008.</p> <p><i>European Journal of Heart Failure</i> 2019, 21(5):665-675.</p>

Source: Table 2.1, pp45-46 of the submission; Section 2A.1, pp1-9 of Section 2A empagliflozin vs. dapagliflozin.docx, Attachment 4 of the submission; Attachment 14 of the submission.

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

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

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in model
<b>Empagliflozin plus SC vs placebo plus SC</b>						
EMPEROR-Reduced	3,730	Phase III, MC, R, DB, PC;  Median duration of follow-up 16 months	Low	<ul style="list-style-type: none"> <li>Age ≥18 years</li> <li>Symptomatic HFrEF with LVEF ≤40%</li> <li>NYHA Class II-IV</li> <li>Elevated NT-proBNP<sup>a</sup></li> <li>eGFR ≥20 mL/min/1.73 m<sup>2</sup></li> <li>On standard care consistent with local and international guidelines</li> </ul>	<ul style="list-style-type: none"> <li>Composite of time to CV death or hospitalisation for HF</li> <li>Time to hospitalisation for HF</li> <li>Time to CV death</li> <li>Total hospitalisations for HF</li> <li>Change in slope of eGFR</li> <li>Time to death from any cause</li> <li>Change in KCCQ-CSS</li> </ul>	KCCQ-CSS scores, all-cause mortality, CV mortality, HF hospitalisation treatment discontinuation, EQ-5D scores, adverse events
<b>Dapagliflozin plus SC vs placebo plus SC</b>						
DAPA-HF	4,744	Phase III, MC, R, DB, PC;  Median duration of follow-up 18.2 months	Low	<ul style="list-style-type: none"> <li>Age ≥18 years</li> <li>Symptomatic HFrEF</li> <li>With LVEF ≤40%</li> <li>NYHA Class II-IV and</li> <li>Elevated NT-proBNP<sup>b</sup></li> <li>eGFR ≥30 mL/min/1.73 m<sup>2</sup></li> <li>On standard care consistent with local and international guidelines</li> </ul>	<ul style="list-style-type: none"> <li>Composite of time to CV death, hospitalisation for HF, or urgent HF visit</li> <li>Time to CV death or hospitalisation for HF</li> <li>CV death or recurrent HF hospitalisations</li> <li>Time to ≥50% decline in eGFR, ESRD or renal death</li> <li>Time to death from any cause</li> <li>Change in KCCQ-TSS</li> <li>Change in EQ-5D-5L</li> </ul>	-

Source: Sections 2.3 and 2.4, pp50-73 of the submission; Sections 2A.3 and 2A.4 pp11-28, and Tables 2.6, p19 and 2.8, p25 of Section 2A empagliflozin vs. dapagliflozin.docx, Attachment 4 of the submission.

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

<sup>a</sup> Ejection Fraction (EF) ≥36% to ≤40%: elevated NT-proBNP at Visit 1 ≥2500 pg/ml for patients without Atrial Fibrillation (AF), or ≥5000 pg/mL for patients with AF; OR EF ≥31% to ≤35%: elevated NT-proBNP at Visit 1 ≥1000 pg/mL for patients without AF, or ≥2000 pg/mL for patients with AF; OR EF ≤30%: elevated NT-proBNP at Visit 1 ≥600 pg/mL for patients without AF, or ≥1200 pg/mL for patients with AF.

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

6.6 The risk of bias was low in both the EMPEROR-Reduced and DAPA-HF trials. Both trials recruited patients with symptomatic HFrEF (NYHA Class II-IV), with an LVEF ≤40%, treated with an SGLT2 inhibitor in addition to local standard care for heart failure (HF), with a mean age of approximately 66 years, and predominantly male (76%) and Caucasian (70%).

6.7 There were differences between the EMPEROR-Reduced trial population and the Australian setting in the risk factors of age, sex, and BMI (Atherton et al. 2018). The Pre-Sub-Committee Response (PSCR) reiterated that the results of the subgroup analyses of the primary composite outcome showed that there was no significant treatment interaction effect for these factors (p = 0.49; p = 0.08; p = 0.17, respectively).

- 6.8 There were some differences between trials in potentially important baseline markers of disease severity and progression. Larger proportions of patients in the EMPEROR-Reduced trial reported less severe HF symptoms (NYHA CLASS II - 75%, Class III - 24%) compared to the DAPA-HF trial (NYHA CLASS II - 68%; Class III - 32%), while patients in the EMPEROR-Reduced trial also reported a higher median baseline NT-proBNP (1,887-1926 pg/mL) compared to DAPA-HF (1,428-1,446 pg/mL), a lower mean baseline LVEF (27%) compared to DAPA-HF (31%) and larger proportions of patients with type 2 diabetes (50%) compared to the DAPA-HF trial (42%). The ESC noted that the likely effects of these differences were bidirectional.
- 6.9 Baseline use of diuretics, beta-blockers and MRAs was similar between trials (EMPEROR-Reduced: diuretic - 95%, beta-blocker - 95%, MRA - 71%; DAPA-HF: diuretic - 93%, beta-blocker - 96%, MRA - 71%), but use of other HF medicines varied between trials (EMPEROR-Reduced: ACEi - 46%, ARB - 28%, ARNi - 19%; DAPA-HF: ACEi - 56%, ARB - 24%, ARNi - 11%).
- 6.10 There were some differences between trials in eligibility criteria (NT-proBNP, minimum eGFR), as well as baseline patient characteristics (geographical region, NYHA Class, median NT-proBNP, mean LVEF, type 2 diabetes) and use of HF medications in standard care (proportion of ACEi/ARB vs ARNi). The ESC again noted that these differences were likely bidirectional.
- 6.11 The PSCR argued that the differences mentioned above were minor, and were unlikely to have had a meaningful impact on the key efficacy outcomes, as illustrated by comparable HRs and the absence of statistical heterogeneity (shown in Zannad et al., 2020), for the similar primary composite outcomes of the two trials.
- 6.12 The submission noted that there is no generally accepted level of clinically important difference for the primary composite outcome of time to the first event of adjudicated cardiovascular death or hospitalisation for heart failure, but noted that in the March 2016 consideration of sacubitril/valsartan for the treatment of chronic HFrEF, the PBAC accepted a clinical claim of superior effectiveness compared to enalapril, based on a hazard ratio of 0.80 (95% CI: 0.73, 0.87; sacubitril/valsartan, PSD, March 2016 PBAC meeting). The PBAC had considered that that size of the benefit was uncertain due to issues with study design and early stopping of PARADIGM-HF (para 7.7, sacubitril/valsartan, PSD, March 2016 PBAC meeting).
- 6.13 For the indirect treatment comparison with dapagliflozin, the submission nominated a noninferiority margin (NIM) of 1.3, derived from an *FDA expert committee advice used to inform Draft Guidance for Industry: Diabetes mellitus* (FDA, 2018; FDA 2018b), for the composite outcome of major adverse cardiovascular events (MACE), including cardiovascular death, myocardial infarction, stroke, and hospitalisation for acute coronary syndrome. The FDA committee guidance related to testing new medicines for the treatment of diabetes for increased cardiovascular risk, and the evaluation raised that this may not be directly applicable to HFrEF and the key composite outcome of time to first cardiovascular death or hospitalisation for heart failure (HF).

- 6.14 It was noted that in the November 2020 consideration of dapagliflozin for the treatment of HFrEF, the ESC considered that a NIM of 1.104 was reasonable for the composite outcome of time to cardiovascular death or hospitalisation for heart failure, in the indirect treatment comparison of dapagliflozin and sacubitril/valsartan (para 6.13, dapagliflozin PSD, November 2020 PBAC meeting). This was derived from the ATMOSPHERE trial (Krum et al, 2011; McMurray, 2016), comparing aliskiren monotherapy to enalapril monotherapy in patients with HFrEF, and was based on the 95-95 method with 50% preservation of the effect of placebo against enalapril in the SOLVD-Treatment trial (1991).
- 6.15 The submission and the PSCR argued that the NIM of 1.104 was not applicable to the ITC of empagliflozin and dapagliflozin, as it was derived from a head-to-head comparison using the 95-95 method with 50% preservation of the comparative effect of placebo, and was unsuitable for ITCs with wider confidence intervals. The submission and the PSCR also noted that the SOLVD-Treatment trial population was not applicable to the eligible population (LVEF of  $\leq 35\%$ , included patients with NYHA Class I heart failure), and that standard care has evolved substantially since the 1991 SOLVD-Treatment trial. The PSCR also noted that an expert advisory board of 13 cardiologists had considered that a NIM of 1.104 would be inappropriate in the context of this ITC. The ESC agreed with the PSCR that the SOLVD-Treatment trial had applicability issues. The ESC noted the EMA guideline on the choice of NIM (p10)<sup>1</sup> states that “selection of the non-inferiority margin is based upon a combination of statistical reasoning and clinical judgement” and it considered that cardiologists would likely agree that no difference in clinical effectiveness would be expected between empagliflozin and dapagliflozin given the results of the respective trials in HFrEF, even if proving noninferiority in an ITC was challenging. The ESC advised that there appears to be broad consensus that the benefits for the SGLT2 inhibitors in HFrEF are a class effect, and this is reflected in clinical guidelines and practice. As such, less importance should be placed on either of the NIMs, neither of which are specific to the population being assessed. The ESC also noted that the NIMs would increase the risk by between 10–30%, and that given the HRs in Table 7 (below), this would not necessarily be considered a significant clinical difference.

### ***Comparative effectiveness***

- 6.16 The table below summarises the results of the primary composite outcome (time to first cardiovascular death or hospitalisation for heart failure) of the EMPEROR-Reduced trial for empagliflozin plus SC compared to placebo plus SC.

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<sup>1</sup> Available from: <https://www.ema.europa.eu/en/choice-non-inferiority-margin>

**Table 4: Results for the primary composite outcome of time to first cardiovascular death or hospitalisation for HF (adjudicated) from the EMPEROR-Reduced trial (ITT; pre-specified hierarchical testing sequence)**

Outcome	Empagliflozin + SC N=1863	Placebo + SC N=1867	Hazard ratio (95% CI) <sup>a</sup>
Composite of time to CV death or HHF <sup>b</sup> n (%)	361 (19.4%)	462 (24.7%)	<b>0.75 (0.65, 0.86)</b>
- HHF as the first event	246 (13.2%)	341 (18.3%)	-
- CV death as the first event	115 (6.2%)	120 (6.4%)	-
Median duration of treatment	16 months		-

Source: Table 2.13, p74 of the submission.

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

<sup>a</sup> Hazard ratios <1 favour empagliflozin. Statistically significant results in bold.

<sup>b</sup> Cox regression model included factors of age, baseline eGFR, region, baseline diabetes status, sex, baseline LVEF, and treatment.

6.17 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: 0.75; 95% CI: 0.65, 0.86), over a median duration of treatment of 16 months.

6.18 The table below summarises the key secondary outcome of occurrence of hospitalisation for heart failure (first and recurrent) in a joint frailty model with a competing risk of cardiovascular death, with the same covariates used for the primary outcome.

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

Outcome	Empagliflozin + SC N=1863	Placebo + SC N=1867	Hazard ratio (95% CI) <sup>a</sup>
<b>Adjudicated HHF (first and recurrent)<sup>b</sup> (joint frailty model)</b>			
Number of HHF events, n	388	553	-
Patients with HHF events, n (%)	246 (13.2%)	342 (18.3%)	<b>0.70 (0.58, 0.85)</b>
patients with HHF then CV death	72 (3.9%)	82 (4.4%)	-
patients with HHF only	174 (9.3%)	260 (13.9%)	-
Patients with CV death only, n (%)	115 (6.2%)	120 (6.4%)	0.90 (0.70, 1.15)

Source: Table 2.14, p77 of the submission.

HHF, hospitalisation for heart failure; ITT, intention to treat; SC, standard care.

<sup>a</sup> Hazard ratios <1 favour empagliflozin. Statistically significant results in bold.

<sup>b</sup> Joint frailty exponent (alpha) 1.09. Joint frailty model included factors of age, region, sex, and baseline eGFR, diabetes status, LVEF.

6.19 Treatment with empagliflozin was associated with a statistically significant improvement in time to first adjudicated hospitalisation for HF (first and recurrent, joint frailty model) compared to placebo over a median duration of treatment of 16 months (hazard ratio: 0.70; 95% CI: 0.58, 0.85), with total number of hospitalisations for HF lower in the empagliflozin group than in the placebo group. The hazard of recurrent hospitalisation for HF was positively correlated with that of cardiovascular death (indicated by a frailty exponent >0).

6.20 The rate of decline in eGFR over a median duration of treatment of 16 weeks was statistically significantly slower in patients treated with empagliflozin plus SC compared to placebo plus SC, with an estimated difference in slope of 1.733 per year (95% CI: 1.100, 2.366). The composite outcome of time to first renal event also favoured empagliflozin (hazard ratio 0.50, 95% CI: 0.32, 0.77).

6.21 The table below summarises the results of the exploratory secondary cardiovascular and renal outcomes of the EMPEROR-Reduced trial (ITT).

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

Outcome	Empagliflozin + SC N=1863	Placebo + SC N=1867	Hazard ratio (95% CI) <sup>a</sup>
First adjudicated HHF (first and recurrent), n (%)	246 (13.2%)	342 (18.3%)	0.69 (0.59, 0.81)
First adjudicated CV death, n (%)	187 (10.0%)	202 (10.8%)	0.92 (0.75, 1.12)
All-cause mortality, n (%)	249 (13.4%)	266 (14.2%)	0.92 (0.77, 1.10)
All cause hospitalisation (first and recurrent), n (%)	688 (36.9%)	796 (42.6%)	0.85 (0.75, 0.95)
Composite renal endpoint <sup>b</sup> n (%)	30 (1.6%)	58 (3.1%)	0.50 (0.32, 0.77)

Source: Table 2.17, p81; Table 2.16, p80; Table 2.18, p83; Table 2.18, p84; and Table 2.20, p86 of the submission.

CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalisation for heart failure; ITT, intention to treat; LVEF, left ventricular ejection fraction; SC, standard care.

<sup>a</sup> Hazard ratios <1 favour empagliflozin

<sup>b</sup> Composite of time to first event of: (i) chronic dialysis ( $\geq 2$  times/week for at least 90 days); (ii) renal transplant; (iii) sustained reduction in eGFR from baseline of  $\geq 40\%$ ; (iv) sustained eGFR  $<15$  mL/min/1.73 m<sup>2</sup> from baseline  $\geq 30$  mL/min/1.73 m<sup>2</sup>, or  $<10$  mL/min/1.73 m<sup>2</sup> from baseline  $<30$  mL/min/1.73 m<sup>2</sup>.

6.22 The results of the exploratory outcomes of the EMPEROR-Reduced trial mostly favoured empagliflozin plus SC, but given the outcomes were exploratory, differences should be considered nominal only. Similar proportions of cardiovascular death and all-cause mortality were reported in both treatment arms, with the upper confidence intervals of the hazard ratios of both outcomes exceeding 1, suggesting no difference in mortality between treatments. However, the ESC noted that the trial was not powered to demonstrate a mortality benefit.

6.23 Treatment with empagliflozin was associated with nominal improvements in the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score, clinical summary score (CSS) and total summary score from baseline to Week 52, with improvement in the KCCQ-CSS demonstrated from Week 12 of treatment in both treatment arms.

6.24 The submission noted that a clinically meaningful improvement in KCCQ-CSS ( $\geq 5$  points) occurred more frequently in the empagliflozin treatment arm (40%) compared to placebo (35.9%; odds ratio 1.23; 95% CI: 1.05, 1.45), and fewer patients in the empagliflozin treatment arm (32.8%) reported a clinically meaningful decrease in KCCQ score ( $\geq 5$  points) compared to placebo (36.1%; odds ratio 0.84; 95% CI: 0.72, 0.99).

### Subgroup analyses

6.25 Across the pre-specified subgroup analyses, the benefit of empagliflozin plus SC in time to first cardiovascular death or hospitalisation for heart failure compared to placebo plus SC was generally consistent with the result reported for the ITT population. However, tests for treatment effect interaction indicated a significant interaction by baseline heart systolic function (LVEF), with empagliflozin associated with a smaller magnitude of effect in patients with LVEF  $>30\%$ ; and by racial subgroup, with empagliflozin associated with a smaller magnitude of effect for White patients.

- 6.26 The PSCR considered that these subgroup analyses should be interpreted with caution as they were not adjusted for multiple testing. The PSCR noted evidence of a consistent treatment effect in patients with preserved ejection fraction (LVEF >40%, including the subgroup LVEF >40 to <50%; EMPEROR-Preserved trial), and also that the European Society of Cardiology Class I, Level A evidence recommendation for use of SGLT2 inhibitors in HFrEF included patients with LVEF between 30 and 40%. The ESC advised that these subgroup analyses should be regarded as exploratory.
- 6.27 The PSCR claimed that the significant treatment effect interaction for the race subgroup may reflect differences in regional health systems (the majority of white patients in the study were from Europe), as well as the small and unequal sample sizes for each of the race subgroups. It was noted that the findings of the EMPA-REG OUTCOME trial which had larger sample sizes and comparable baseline characteristics to the EMPEROR-Reduced trial showed no treatment interaction effect by race (p=0.43).
- 6.28 Results of the subgroup analyses by treatment with or without ARNi at baseline were generally consistent with the results reported for the overall ITT population. However, results of the subgroup analyses for time to cardiovascular death or all-cause mortality were less favourable for empagliflozin in the subgroup without ARNi at baseline, although the tests for treatment effect interaction were not significant.

### Indirect treatment comparison with dapagliflozin

- 6.29 The table below summarises the indirect treatment comparison (ITC) of empagliflozin plus SC versus dapagliflozin plus SC for the key composite outcome of time to first of cardiovascular death or hospitalisation for heart failure.

**Table 7: Summary of the indirect comparison of empagliflozin plus SC versus dapagliflozin plus SC for the key composite outcome of time to first cardiovascular death or hospitalisation for HF (ITT)**

Trial	Empagliflozin + SC n/N (%)	Placebo + SC n/N (%)	Dapagliflozin + SC n/N (%)	Hazard Ratio (95% CI)
<b>Empagliflozin + SC vs dapagliflozin + SC: similar outcome definitions (time to CV death or HHF)<sup>a</sup></b>				
EMPEROR-Reduced	361/1863 (19.4%)	462/1867 (24.7%)		<b>0.75 (0.65, 0.86)</b>
DAPA-HF		495/2371 (20.9%)	382/2373 (16.1%)	<b>0.75 (0.65, 0.85)</b>
Indirect treatment comparison for empagliflozin + SC versus dapagliflozin + SC				1.00 (0.82, 1.21)
<b>Empagliflozin + SC vs dapagliflozin + SC: sensitivity analysis using primary outcomes<sup>b</sup></b>				
EMPEROR-Reduced	361/1863 (19.4%)	462/1867 (24.7%)		<b>0.75 (0.65, 0.86)</b>
DAPA-HF		502/2371 (21.2%)	386/2373 (16.3%)	<b>0.74 (0.65, 0.85)</b>
Indirect treatment comparison for empagliflozin + SC versus dapagliflozin + SC				1.01 (0.84, 1.23)

Source: Table 2.19, p43 of the submission. Note: Statistically significant results in bold.

CI, confidence interval; CV, cardiovascular; HF, heart failure; HHF, hospitalisation for heart failure; ITT, intention to treat; SC, standard care.

<sup>a</sup> Key secondary outcome for the DAPA-HF trial of time to first CV death or HHF.

<sup>b</sup> Primary composite outcome for the DAPA-HF trial of time to first CV death, HHF, or urgent HF visit.

- 6.30 Results of the ITC of empagliflozin plus SC versus dapagliflozin plus SC for the primary composite outcome showed no statistically significant difference between treatments (hazard ratio 1.00; 95% CI: 0.82, 1.21). The upper 95% confidence interval for the ITC did not exceed the nominated noninferiority margin of 1.3. However, the upper 95% confidence interval of the ITC exceeded a noninferiority margin of 1.104 considered

reasonable by ESC at the November 2020 PBAC meeting (para 6.13, dapagliflozin, PSD, November 2020 PBAC meeting).

- 6.31 There were no statistically significant differences for the ITCs based on secondary outcomes. The lack of a statistically significant difference may not be sufficient to establish noninferiority as the 95% confidence intervals may include clinically important differences. However, as noted above in the Clinical trials section, the benefit of the SGLT2 inhibitors are broadly considered to be a class effect. The evaluation considered that the results of the ITCs should be interpreted with caution due to differences between the trials in patient characteristics and standard care treatments. The ESC agreed that any ITC results should be interpreted with caution, but also noted that the differences between trials were bidirectional.

### Comparative harms

- 6.32 The table below summarises the results of the key safety outcomes for the EMPEROR-Reduced trial comparing empagliflozin plus SC with placebo plus SC.

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

Adverse events, n (%)	Empagliflozin + SC (N=1863)	Placebo + SC (N=1863)
Patients with any adverse events	1420 (76.2%)	1463 (78.5%)
Severe adverse events	459 (26.2%)	502 (26.9%)
Serious adverse events	772 (41.4%)	896 (48.1%)
Drug-related adverse events	283 (15.2%)	227 (12.2%)
Adverse events leading to discontinuation	322 (17.3%)	328 (17.6%)
Adverse events resulting in death	181 (9.7%)	181 (9.7%)
Adverse events requiring hospitalisation	596 (32.0%)	688 (36.9%)

Source: Table 2.21, p89 of the submission.

SC, standard care.

- 6.33 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 hospitalisation (mostly related to hospitalisation for heart failure).
- 6.34 The most common adverse events of special interest reported in patients treated with empagliflozin plus SC were volume depletion (10.6%), acute renal failure (9.4%), hypotension (9.4%), and urinary tract infection (4.9%). Similar incidences of adverse events of special interest were reported in patients receiving placebo plus SC.
- 6.35 The proportions of patients reporting adverse events were generally similar between subgroups with or without baseline ARNi therapy. However, larger proportions of patients treated with empagliflozin with baseline ARNi therapy reported volume depletion and hypotension compared to placebo as well as compared to patients without baseline ARNi therapy. Larger proportions of patients treated with placebo with baseline ARNi therapy reported worsening renal function and acute kidney injury compared to empagliflozin as well as compared to patients without baseline ARNi therapy.

6.36 The submission also presented ITCs of empagliflozin plus SC versus dapagliflozin plus SC for adverse events of interest.

**Table 9: Summary of the indirect treatment comparison of safety outcomes of interest in the EMPEROR-Reduced and DAPA-HF and trials (nominal; treated set)**

Outcome	Empagliflozin + SC vs placebo + SC RR (95% CI)	Dapagliflozin + SC vs placebo + SC RR (95% CI)	Indirect comparison RR (95% CI)
Adverse events leading to discontinuation	0.98 (0.85, 1.13)	0.96 (0.74, 1.23)	1.02 (0.76, 1.40)
Ketoacidosis <sup>a</sup>	0.61 (0.29, 1.29)	7.00 (0.36, 135.44)	0.09 (0.004, 1.85)
Fracture	1.07 (0.71, 1.62)	0.98 (0.66, 1.45)	1.09 (0.62, 1.93)
Amputation <sup>b</sup>	1.30 (0.57, 2.96)	1.08 (0.50, 2.37)	1.20 (0.39, 3.74)
Hypoglycaemia <sup>c</sup>	0.96 (0.57, 1.63)	1.00 (0.25, 3.99)	0.96 (0.22, 4.22)
Volume depletion	1.07 (0.89, 1.30)	1.10 (0.90, 1.35)	0.97 (0.74, 1.29)

Source: Table 2.22, p55 of the submission.

Abbreviations: CI, confidence interval; RR, risk ratio; SC, standard care.

<sup>a</sup> EMPEROR-Reduced included diabetic ketoacidosis by broad BlcMQ definition. DAPA-HF included all reported cases adjudicated as definite or probable.

<sup>b</sup> Included amputations vary between trials, DAPA-HF definition broader than EMPEROR-Reduced.

<sup>c</sup> EMPEROR-Reduced and DAPA-HF definitions of hypoglycaemia vary.

6.37 The submission acknowledged that there were differences between trials in terms of adverse event coding (ketoacidosis, fractures + volume depletion) and definitions of events between trials (ketoacidosis, amputations, hypoglycaemia).

### **Benefits/harms**

6.38 On the basis of the direct evidence presented in the submission, for every 100 patients treated with empagliflozin plus SC in comparison with placebo plus SC for a median of 16 months:

- Approximately 5 fewer patients would die due to cardiovascular causes or be hospitalised for heart failure. This difference was due to fewer heart failure hospitalisations.
- Approximately 3 additional patients would experience a drug-related adverse event.
- Approximately 7 fewer patients would experience a serious adverse event.

6.39 A comparison of benefits and harms for empagliflozin plus SC versus dapagliflozin plus SC has not been presented, given the claim of noninferior effectiveness and safety.

### **Clinical claim**

6.40 The submission described empagliflozin plus SC as superior in terms of effectiveness compared with placebo plus SC and noninferior in terms of safety compared to placebo plus SC, in the treatment of HFrEF.

6.41 This therapeutic conclusion was adequately supported by the clinical evidence presented in the submission. However, the applicability of the EMPEROR-Reduced results to Australian clinical practice was less certain, given differences in risk factors of age, sex and BMI, and significant treatment effect interactions associated with baseline LVEF and race subgroups.

- 6.42 The submission described empagliflozin plus SC as noninferior in terms of effectiveness and safety compared with dapagliflozin plus SC, in the treatment of HFrEF.
- 6.43 The evaluation identified some residual uncertainty associated with this therapeutic conclusion:
- There were some differences between the EMPEROR-Reduced and DAPA-HF trials in eligibility criteria (NT-proBNP, minimum eGFR), baseline patient characteristics (geographical region, NYHA Class, median NT-proBNP, mean LVEF, type 2 diabetes), baseline use of heart failure medications in standard care (ACEi, ARB, ARNi), and duration of follow-up (median 18.2 months versus 16 months). However, the ESC noted that these differences were bidirectional.
  - The clinical claim of noninferior effectiveness based on the ITC of empagliflozin plus SC versus dapagliflozin plus SC, for the primary composite outcomes, was based on the nominated noninferiority margin of 1.3. Applying the noninferiority margin of 1.104 previously considered reasonable by ESC for indirect comparisons in the HFrEF population at the November 2020 PBAC meeting (para 6.13, dapagliflozin, PSD, November 2020 PBAC meeting), empagliflozin plus SC did not demonstrate noninferiority compared to dapagliflozin plus SC. The ESC noted that there is no agreed noninferiority margin in this population and that, based on clinical consensus, the benefit is likely to be a class effect for empagliflozin and dapagliflozin.
- 6.44 The PBAC agreed with the ESC that the claim of noninferior effectiveness and safety was reasonable compared with dapagliflozin, noting that neither of the NIMs (1.3 or 1.104) were specific to the population being assessed, but that there appears to be broad consensus that the benefits for the SGLT2 inhibitors in HFrEF are a class effect, which is reflected in clinical guidelines and practice.

### ***Economic analysis***

- 6.45 The submission presented a modelled economic evaluation of empagliflozin plus SC versus standard care alone, in patients with HFrEF. The economic analysis was based on the results of the EMPEROR-Reduced trial, with additional modelled data. The type of economic evaluation presented was a cost-utility analysis.
- 6.46 A cost-minimisation analysis to dapagliflozin was presented during the evaluation, with equi-effective doses of dapagliflozin 10 mg per day and empagliflozin 10 mg per day.

**Table 10: Key components of the economic evaluation**

Component	Summary
Treatments	Empagliflozin versus standard care (including ACE inhibitors, ARBs, beta blockers, mineralocorticoid receptor antagonists, and angiotensin receptor-neprilysin inhibitors).
Time horizon	15 years in the model base case versus median follow-up of 16 months in the EMPEROR-Reduced trial
Outcomes	Life years; quality adjusted life years
Methods used to generate results	Markov state transition model
Health states	KCCQ-CSS quartiles and dead (CV and non-CV)
Cycle length	One month
Transition probabilities	<p>KCCQ-CSS transitions: individual patient data from EMPEROR-Reduced were used to derive monthly transitions between KCCQ-CSS health states for three time periods (baseline to Week 12, Week 12 to Week 32, Week 32 to Week 52). Transition probabilities from Week 32 to Week 52 were used for the remaining time horizon (up to 15 years).</p> <p>CV death transitions were based on Kaplan-Meier time to CV death curves from EMPEROR-Reduced over 16 months, extrapolated to 15 years based on a Weibull function using a single model, with treatment and KCCQ-CSS quartiles as covariates.</p> <p>Non-CV mortality transitions were derived from estimates of all-cause mortality minus estimates of CV mortality. All-cause mortality was based on Kaplan-Meier time to all-cause death curves from EMPEROR-Reduced over 16 months, extrapolated to 15 years based on a Weibull function using a single model, with treatment and KCCQ-CSS quartiles as covariates. 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).</p> <p>Empagliflozin treatment discontinuation was based on an exponential function fitted to the Kaplan-Meier time to treatment discontinuation curve (censored for death) from EMPEROR-Reduced, with KCCQ-CSS quartiles as covariates, extrapolated to 15 years.</p> <p>Monthly probabilities of heart failure hospitalisation were derived using a Poisson model fitted to the observed data from EMPEROR-Reduced with treatment and KCCQ-CSS quartiles as covariates.</p> <p>The monthly probabilities of adverse events used in the modelled economic evaluation were derived from the rate per 100 patient years of adverse events of special interest from the EMPEROR-Reduced trial. 86.0% of incremental costs and 81.7% of incremental QALYs were accrued in the extrapolated period beyond 18 months.</p>
Costs	<p>The cost of empagliflozin was based on the proposed DMPQ and 100% adherence.</p> <p>The cost of standard care was based on: the distribution of use of heart failure medicine classes in EMPEROR-Reduced; the recommended dose for each medicine based on its PI; the DPMQ and pack size from the PBS Schedule; and 100% adherence.</p> <p>Disease management costs were based on resource use estimates from Ford 2012, with unit costs based on MBS items. Ford 2012 presented resource use by NYHA class and the submission assumed that these would apply to the KCCQ-CSS quartiles (e.g. NYHA class IV corresponds to KCCQ-CSS quartile 1).</p> <p>Heart failure hospitalisation costs were based on AR-DRG costs for heart failure.</p> <p>Cardiovascular death costs were based on AR-DRG costs for heart failure, stroke, and myocardial infarction.</p> <p>Adverse event costs were weighted by severity, 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.</p>

Component	Summary
Health related quality of life	<p>EQ-5D-5L scores from EMPEROR-Reduced were mapped to EQ-5D-3L scores using the methodology outlined in Hernandez 2017, using the UK value set. The ESC noted that no justification was provided as to why Australian values were not used.</p> <p>KCCQ-CSS health state utilities were derived from a linear mixed regression equation fitted to EQ-5D-3L data from EMPEROR-Reduced. Utilities were adjusted so that utilities did not exceed the utility of the UK general population aged 60 to 69 (KCCQ-CSS quartile 4, 0.7740; quartile 3, 0.7101; quartile 2, 0.6370; quartile 1, 0.5201).</p> <p>Disutilities of heart failure hospitalisation were also derived from the linear mixed regression equation fitted to data from EMPEROR-Reduced. 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 &lt;1 month, -0.03193; 1 to &lt;2 months, -0.03970; 2 to &lt;4 months, -0.02902; 4 to &lt;12 months -0.01453).</p> <p>Adverse event disutilities were derived from multiple published sources (Dapagliflozin NICE submission, Sullivan 2016, Sullivan 2006) ranging from to -0.003 for hepatic injury to -0.149 for bone fracture); assumed to apply for 1 month.</p>

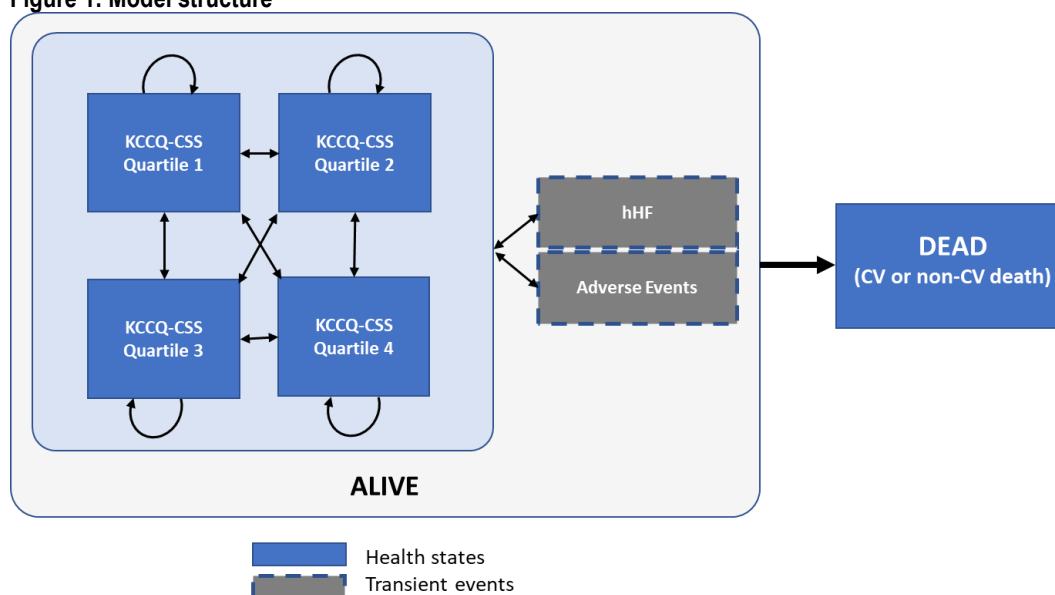
Source: Sections 3.3 to 3.6 of the submission

ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; 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; NYHA, New York Heart Association; PBS, Pharmaceutical Benefits Scheme; PI, product information

6.47 The economic model had a 15-year time horizon, which the submission stated was consistent with survival in patients with heart failure (based on a systematic review and meta-analysis of survival in heart failure; Jones 2019) and was appropriate to capture the clinical and economic consequences of empagliflozin plus SC and placebo plus SC. The pooled survival rates from the systematic review and meta-analysis were 86.5% at 1 year, 56.7% at 5 years, and 34.9% at 10 years. Given the proportion of subjects alive at 10 years, a 15-year time horizon may not be sufficient to capture the lifetime costs and consequences associated with empagliflozin plus SC versus SC, however a longer time horizon would be associated with additional uncertainty given the extrapolation of outcomes based on a median duration of follow-up of 16 months in the EMPEROR-Reduced trial. The PSCR considered the 15-year time horizon was conservative, as approximately one third of patients with HF survive to 10 years. In addition, it considered that the ICER was not significantly impacted when the time horizon was set to 20 years or lifetime.

6.48 The figure below illustrates the structure of the economic evaluation.

Figure 1: Model structure



Source: Figure 3.4, p167 of the submission

CV, cardiovascular; hHF, hospitalisation due to heart failure; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score

- 6.49 Subjects could begin the model in one of the four KCCQ-CSS quartile health states. During each one-month cycle, subjects could 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 could experience hospitalisation due to heart failure or treatment-related adverse events. Subjects in the empagliflozin arm could discontinue drug treatment in each cycle. The model applied higher rates of heart failure hospitalisation, and CV and non-CV mortality to patients with poorer KCCQ-CSS scores (based on quartiles). Heart failure hospitalisations were associated with a cost and disutility, but did not alter health state transitions and did not affect mortality rates, which was unlikely to reflect the disease pathway.
- 6.50 The PSCR and pre-PBAC response considered that although HHF may impact health state transitions and mortality rates, incorporating HHF as a separate health state would have significantly increased the complexity of the model. While it recognised that there was no explicit consideration of HHF impacts on health state transitions and mortality in the current model structure, it claimed that any HHF that resulted in a change in health state or death in EMPEROR-Reduced was implicitly captured in the health state transition matrices and/or the mortality equations (as patients move to lower KCCQ-CSS quartiles, they progress in their disease and as a result their risk of hospitalisation and mortality increases). The ESC considered that this may be true for the within trial period, but it was less likely over the extrapolated period.
- 6.51 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 HFrEF. The submission claimed that the KCCQ is a better measure of disease severity compared with NYHA class, but no justification was provided in the submission. In the NICE assessment of dapagliflozin for HFrEF, clinical experts stated that NYHA class is more subjective and less sensitive to changes in patient symptoms than the KCCQ tool. The submission noted that, in assessing the dapagliflozin HFrEF submission, the NICE evaluation committee stated that the KCCQ tool is a reasonable tool to classify disease severity and is appropriate for decision making. The impact of the different KCCQ summary scores used to define health states (KCCQ-CSS in the submission; KCCQ-TSS in the NICE dapagliflozin submission) was unclear.

- 6.52 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-Reduced to derive monthly transitions between NYHA class health states (see Table 13).
- 6.53 Alternative analyses were also presented based on the subgroups by baseline ARNi use. These analyses used patient characteristics based on the baseline ARNi use subgroups in EMPEROR-Reduced (used to inform initial health state distribution, background mortality, health state utilities and drug costs). The Weibull risk equations for cardiovascular mortality and all-cause mortality, and Poisson model for estimating heart failure hospitalisations were also refitted using data from the subgroups by baseline ARNi use.

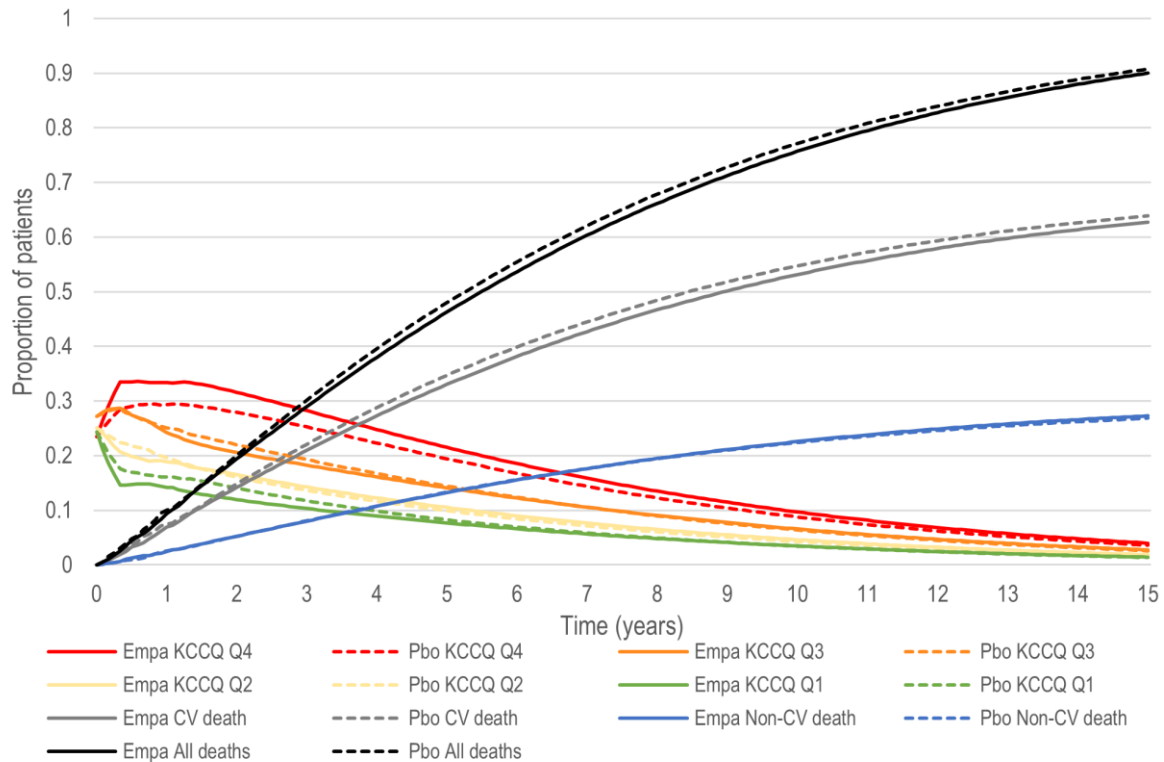
**Table 11: Key drivers of the model**

Description	Method/Value	Impact
Modelled mortality benefit	<p>The model assumed differences in time to cardiovascular death favouring empagliflozin that were not consistent with the available clinical data (see Table 6 above).</p> <p>In the model, a cardiovascular mortality benefit for empagliflozin was generated from improved survival within each KCCQ-CSS health state (with the exception of KCCQ-CSS quartile 2), 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.</p> <p>The impact of no survival benefit associated with empagliflozin treatment could not be tested during the evaluation due to the model structure with estimates of cardiovascular mortality curves derived separately for KCCQ-CSS health states.</p> <p>The ESC noted the PSCR reiterated the clinical plausibility of mortality benefit with empagliflozin, and ESC considered the trial data was likely limited in being powered to assess this outcome given the sample size and the limited follow up of a median 16 months.</p>	High, favours empagliflozin
KCCQ-CSS quartile health state transitions	<p>The model assumed that transition probabilities between KCCQ-CSS quartile health states, derived from individual patient data from EMPEROR-Reduced between 9 and 12 months, are constant from month 9 to the end of the 15-year model time horizon.</p> <p>Analysis of individual patient data indicates that patients in both treatment arms experience initial improvement in health status, followed by stabilisation. It was unclear whether transitions derived from the 9-12-month period adequately reflect longer term health outcomes in a progressive disease. The PSCR acknowledged the absence of long term KCCQ-CSS data. However, it stated that based on the trial KCCQ data, the variation in the transition probabilities between Months 4-8 and Months 9+ was much less than the variation between Months 1-3 and Months 4-8, which it suggested meant that the transition probabilities were relatively stable over time.</p>	Unclear
QALY loss associated with hospitalisation for heart failure	<p>The disutility associated with heart failure hospitalisation, derived from EMPEROR-Reduced 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 derived HHF disutilities from the linear regression equation to 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 &lt;4 months was multiplied by 2 months) rather than the proportion of a year spent in the health state (e.g. <math>\times 2/12</math> months). A disutility of 0.1 over a year, for example, should generate a QALY loss of 0.1 QALYs (<math>=0.1 \times 12/12</math>), not 1.2 QALYs (<math>=0.1 \times 12</math>). This resulted in an overestimate of the QALY loss associated with heart failure hospitalisation. 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 PSCR claimed that the estimates generated from the linear mixed regression equation were not disutilities, but monthly QALY losses. The ESC noted the disutility estimates for heart failure hospitalisation and adverse events were derived from the same linear mixed regression equation, however, as stated above, the approach used to calculate the QALY loss associated with heart failure hospitalisation was inconsistent with the approach used to calculate disutilities associated with adverse events.</p>	Moderate, favours empagliflozin

Source: Constructed during the evaluation with reference to Section 3 of the submission and 'Att\_10\_Jardiance (empagliflozin) HFrEF Economic Evaluation' spreadsheet provided with the submission

6.54 The figure below presents the model traces for empagliflozin plus SC and placebo plus SC arms.

Figure 2: Model trace for empagliflozin plus standard care and placebo plus standard care



Source: Constructed during the evaluation using 'Att\_10\_Jardiance (empagliflozin) HFrEF Economic Evaluation' spreadsheet provided with the submission

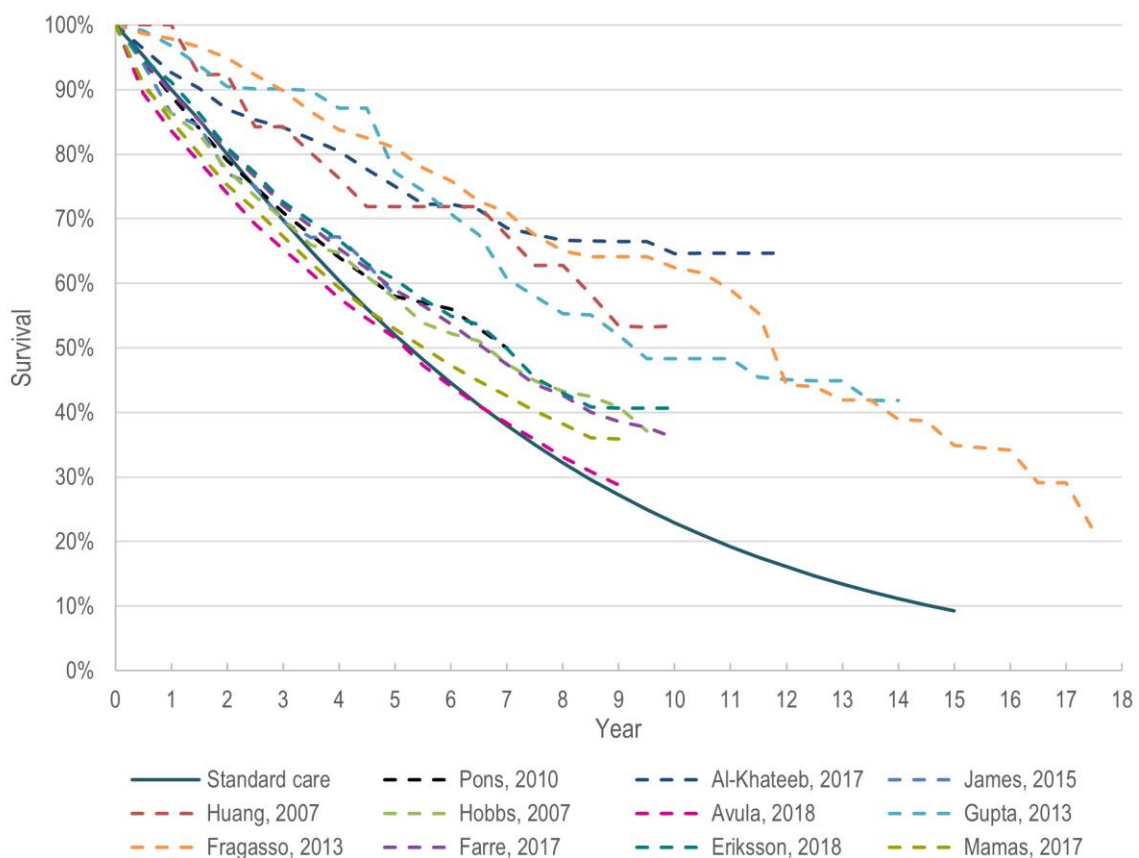
CV, cardiovascular; Empa, empagliflozin plus standard care; KCCQ Q1-4, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score Quartiles 1 to 4; Pbo, placebo plus standard care

- 6.55 The model trace indicated that empagliflozin was associated with a survival benefit, predominantly due to a reduction in cardiovascular deaths. This was not supported by the results of the EMPEROR-Reduced trial, which did not demonstrate a 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 SC arm compared to placebo plus SC, indicating better health status over the model duration. Ninety percent of patients had died by 15 years in the model. The ESC noted the PSCR reiterated the clinical plausibility of a mortality benefit with empagliflozin. The ESC further noted that based on the hierarchical tests performed in the EMPEROR-Reduced trial, the sample size, and the limited follow up of a median 16 months, the trial was not powered to assess this outcome.
- 6.56 The model estimated that on average, patients treated with empagliflozin plus SC would experience 1.10 heart failure hospitalisations, compared with 1.32 hospitalisations in patients treated with standard care alone over 15 years.
- 6.57 The model estimated that 79.4% of empagliflozin plus SC patients would remain on empagliflozin treatment at 1 year, which decreased to 29.4% at 5 years (54.7% of those remaining alive) and 7.7% at 10 years (31.7% of those remaining alive). At the

end of the model, 1.9% of patients remained on empagliflozin (18.7% of those remaining alive).

- 6.58 The submission performed external validation of modelled overall survival in the standard care arm of the model with Kaplan-Meier estimates from selected studies included in a systematic review of survival in patients with heart failure (studies that recruited patients from the year 2000 onwards; studies that reported survival for patients with HFrEF; Jones 2019, shown in figure below). No details were provided about the inclusion/exclusion of studies in the relevant subgroups of the systematic review, and the methods used to extract data from the Kaplan-Meier curves in the individual studies were not reported.

**Figure 3: Modelled standard care survival versus individual studies from Jones 2019 systematic review**



Source: Figure 3.20, p206 of the submission

- 6.59 The submission claimed that, although a number of studies report more favourable survival rates, it was reasonable to conclude that the model was externally valid, albeit on the lower range of reported survival in the published literature. The lower survival for standard care patients estimated in the model compared with published estimates, particularly beyond five years, suggested poor external validity of the model.
- 6.60 The results of the stepped economic evaluation are summarised in the table below. Step 1 of the submission’s stepped economic evaluation, based on a 33-month

duration, could not be replicated. During the evaluation, an alternative Step 1 was used, based on the median follow-up of EMPEROR-Reduced (consistent with the use of Kaplan-Meier curves to inform mortality prior to extrapolation) and including drug costs only. Further, during 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 12: Results of the stepped economic evaluation**

Step and component	Empagliflozin+SC	Placebo+SC	Increment
<b>Step 1: modelled analysis based on EMPEROR-Reduced median follow-up (16 months) and drug costs only <sup>a</sup></b>			
Costs (\$)		\$2,021	
Heart failure hospitalisations	0.1976	0.2584	-0.0608
Deaths	0.1228	0.1251	-0.0023
Life years	1.2148	1.2087	0.0061
Incremental cost per heart failure hospitalisation avoided			<sup>1</sup>
Incremental cost per death avoided			<sup>2</sup>
Incremental cost per life year gained			<sup>3</sup>
<b>Step 2: time horizon extended to 15 years</b>			
Costs (\$)		\$8,475	
Life years	5.2001	5.0700	0.1302
Incremental cost per life year gained			<sup>4</sup>
<b>Step 3: disease management, heart failure hospitalisation, CV death and adverse event costs included</b>			
<b>Step 3a: disease management costs included <sup>a</sup></b>			
Costs (\$)		\$12,171	
Life years	5.2001	5.0700	0.1302
Incremental cost per life year gained			<sup>4</sup>
<b>Step 3b: heart failure hospitalisation costs included <sup>a</sup></b>			
Costs (\$)		\$20,571	
Life years	5.2001	5.0700	0.1302
Incremental cost per life year gained			<sup>1</sup>
<b>Step 3c: CV death costs included <sup>a</sup></b>			
Costs (\$)		\$25,149	
Life years	5.2001	5.0700	0.1302
Incremental cost per life year gained			<sup>1</sup>
<b>Step 3d: adverse event costs included</b>			
Costs (\$)		\$30,923	
Life years	5.2001	5.0700	0.1302
Incremental cost per life year gained			<sup>1</sup>
<b>Step 4: utilities applied to time in health states, disutilities applied for heart failure hospitalisation, adverse events</b>			
<b>Step 4a: utilities applied to time in health states <sup>a</sup></b>			
Costs (\$)		\$30,923	
QALYs	3.5963	3.4779	0.1184
Incremental cost per QALY gained			<sup>1</sup>
<b>Step 4b: disutility applied for heart failure hospitalisation <sup>a</sup></b>			
Costs (\$)		\$30,923	
QALYs	3.4096	3.2502	0.1594
Incremental cost per QALY gained			<sup>1</sup>
<b>Step 4c: disutilities applied for adverse events</b>			
Costs (\$)		\$30,923	
QALYs	3.4033	3.2442	0.1590
Incremental cost per QALY gained			<sup>1</sup>

Source: Table 3.28, p 208 of the submission; 'Att\_10\_Jardiance (empagliflozin) HFrEF Economic Evaluation' spreadsheet provided with the submission

QALY, quality adjusted life year; SC, standard care

<sup>a</sup> Corrected (step 1) /stepped out (steps 3a-c and 4a-b) during evaluation.

The redacted values correspond to the following ranges:

<sup>1</sup> \$5,000 to < \$15,000

<sup>2</sup> \$355,000 to < \$455,000

<sup>3</sup> \$135,000 to < \$155,000

<sup>4</sup> \$15,000 to < \$25,000

- 6.61 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.
- 6.62 Based on the modelled economic evaluation, treatment with empagliflozin plus SC was associated with an incremental cost per QALY gained of \$5,000 to < \$15,000 compared to standard care alone for the treatment of patients with HFrEF (this was based on the published price of sacubitril/valsartan, a component of standard of care, which has a Special Pricing Arrangement).
- 6.63 Results based on the subgroup of patients not receiving an ARNi as background therapy, and the subgroup of patients receiving an ARNi as background therapy were \$5,000 to < \$15,000 and \$5,000 to < \$15,000 per QALY gained, respectively (again, based on the published price of sacubitril/valsartan).
- 6.64 The results of key sensitivity analyses are summarised below. Results were not sensitive to the choice of parametric functions used to inform mortality and treatment discontinuation, or the inclusion of adverse event costs and disutilities.

Table 13: Results of key sensitivity analyses

Analysis	Incremental cost (\$)	Incremental QALYs	ICER
<b>Base case</b>		<b>0.1590</b>	
<b>Time horizon (base case 15 years)</b>			
- 10 years		0.1374	
- 20 years		0.1667	
<b>Health states (base case health states based on KCCQ-CSS quartiles; transitions based on EMPEROR-Reduced individual patient data)</b>			
- empagliflozin transitions set equal to placebo transitions <sup>a</sup>		0.0652	
- placebo transitions set equal to empagliflozin transitions <sup>a</sup>		0.0654	
- health states based on NYHA class		0.0847	
<b>Heart failure hospitalisation rate (base case derived using Poisson model fitted to EMPEROR-Reduced data; monthly probabilities vary by KCCQ-CSS state and treatment)</b>			
Halve incremental difference between empagliflozin and placebo <sup>a</sup>		0.1391	
<b>Disease management costs (base case KCCQ-CSS quartile 4 \$48.21/cycle; quartiles 1-3 \$67.58/cycle)</b>			
- increase by 50% <sup>a</sup>		0.1590	
- decrease by 50% <sup>a</sup>		0.1590	
<b>Heart failure hospitalisation costs (base case \$7,906 per event)</b>			
- increase by 50% <sup>a</sup>		0.1590	
- decrease by 50% <sup>a</sup>		0.1590	
<b>CV death costs (base case \$9,150 applied to all CV deaths)</b>			
- CV death costs applied to 50% of CV deaths		0.1590	
- No CV death costs		0.1590	
<b>Health state utilities (base case estimates from EMPEROR-Reduced, with general population utility correction)</b>			
- EMPEROR-Reduced estimates, no general population correction		0.1700	
- NICE dapagliflozin estimates (general population correction)		0.1576	
- NICE dapagliflozin estimates (no general population correction)		0.1653	
<b>Heart failure hospitalisation QALY loss (base case 0.24591, incorrectly applied as 0.2143)</b>			
- correcting error in referencing cells (QALY loss 0.2492) <sup>a</sup>		0.1651	
- alternative estimate (QALY loss 0.0205) <sup>a</sup>		0.1220	
- 50% reduction (QALY loss 0.1230) <sup>a</sup>		0.1416	
- 75% reduction (QALY loss 0.0615) <sup>a</sup>		0.1298	
<b>Discount rate (base case 5% for costs and benefits)</b>			
- 0%		0.2083	
- 3.5%		0.1716	

Source: Table 3.31, pp212-213 of the submission; 'Att\_10\_Jardiance (empagliflozin) HFrEF Economic Evaluation' spreadsheet provided with the submission

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

<sup>a</sup> Analyses conducted during evaluation.

The redacted values correspond to the following ranges:

<sup>1</sup> \$5,000 to < \$15,000

<sup>2</sup> \$0 to < \$5,000

- 6.65 The impact of no survival benefit associated with empagliflozin treatment (consistent with clinical evidence) could not be 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 PSCR stated that the impact of no survival benefit associated with empagliflozin could be tested in the model by removing the treatment term in the all-cause and CV mortality equations; however, this would still generate a survival advantage for empagliflozin given different survival

curves are generated for each KCCQ-CSS health state, and the model generates differences between treatment arms in KCCQ-CSS health state membership.

- 6.66 The results were most sensitive to the heart failure hospitalisation rate, differences between treatment arms in KCCQ-CSS health state transitions, the use of NYHA health states and transitions, the QALY loss associated with heart failure hospitalisation, and heart failure hospitalisation costs. The submission claimed that the results of the NYHA class sensitivity analysis should be viewed in the context of the ‘bluntness’ of physician-based NYHA assessment, given it is more subjective and less sensitive to changes in patient functioning and well-being than patient-reported KCCQ-CSS.

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

- 6.67 The empagliflozin drug cost per patient per year was \$731.72, based on 12.175 scripts per patient 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.
- 6.68 The cost of empagliflozin in the economic analysis includes estimates of the costs of standard care (\$1,671.72 per year), however, these costs were not included in the financial estimates.

**Table 14: Drug cost per patient per year for empagliflozin**

	<b>EMPEROR-Reduced trial</b>	<b>Economic model</b>	<b>Financial estimates</b>
Daily dose	10 mg daily	10 mg daily	10 mg daily
Cost per pack of 30 tablets (proposed DPMQ)	-	\$60.10 <sup>a</sup>	\$60.10 <sup>a</sup>
Adherence	95.1% <sup>b</sup>	100%	95.1% <sup>b</sup>
Number of scripts per year	-	12.175 (=365.25/30 × 100%)	11.578 (=365.25/30 × 95.1%)
Cost per year	-	\$731.72	\$695.86
Proportion of patients on treatment (persistence)	At a median follow-up of 16 months, 73.3% of patients in the empagliflozin arm remained on treatment.	Year 1: 87.6% <sup>c</sup> Year 2: 77.4% Year 3: 68.8% Year 4: 61.3% Year 5: 54.7% Year 6: 49.0%	100%

Source: Table 2.4, p54 of the submission; ‘Att\_10\_Jardiance (empagliflozin) HFrEF Economic Evaluation’ spreadsheet provided with the submission; ‘Att\_13\_Jardiance (empagliflozin) HFrEF - UCM\_final’ spreadsheet provided with the submission  
DPMQ, dispensed price for maximum quantity.

<sup>a</sup> DPMQ for empagliflozin was updated by the evaluation to account for July 2021 changes in PBS fees and mark-ups

<sup>b</sup> Derived from a post hoc analysis of the EMPEROR-Reduced trial (Attachment 6 of the submission)

<sup>c</sup> Estimates based on the proportion of surviving patients on treatment

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

- 6.69 This submission was not considered by DUSC. The submission presented an epidemiological approach to estimate the utilisation and financial impacts associated with the PBS listing of empagliflozin for the treatment of HFrEF over 6 years.
- 6.70 The submission noted that the PBAC had considered a submission for dapagliflozin for HFrEF at the November 2020 PBAC meeting, using an epidemiological approach to estimate the predicted use and financial implications associated with the PBS listing

of an SGLT2i for the treatment of HFrEF. Therefore, the submission included estimates derived from the November 2020 dapagliflozin PSD, adjusted to account for comments by the PBAC and the DUSC.

- 6.71 Dapagliflozin for HFrEF was subsequently considered by the PBAC at the July 2021 meeting (deferred), and the September 2021 meeting (recommended). The PBAC considered that the listing of dapagliflozin would be cost-effective at the price proposed in the July 2021 pre-PBAC response, and that the estimates were broadly reasonable, and would be an appropriate basis for a Risk Sharing Arrangement (RSA) for this indication (PBAC Outcomes, September 2021 Intracycle meeting).
- 6.72 The empagliflozin submission also commissioned a 10% PBS longitudinal sample analysis (scaled up to 100%), to estimate the proportions of patients with heart failure treated with heart failure medicines, and the proportions of heart failure patients likely to be treated with an SGLT2i prior to being treated for heart failure.

**Table 15: Key inputs for financial estimates**

Parameter	Value applied and source	Comment
Prevalence of heart failure, Australia	2.199 per 100 persons, reported by Liew et al., 2020 (SHAPE study)	Based on DUSC comments (para 6.60, dapagliflozin PSD, November 2020 PBAC meeting). This may be reasonable.
Proportion of patients with LVEF ≤40%	60%. Midpoint of the proportions reported in the SHAPE (62%) and SNAPSHOT-HF (58%) studies	Based on DUSC comments (para 6.60, dapagliflozin PSD, November 2020 PBAC meeting).
Proportion of patients with NYHA class II-IV	95%. Proportion of NYHA Class II-IV heart failure from the July 2016 Sacubitril/ valsartan submission	Based on the dapagliflozin November 2020 submission (para 6.57, dapagliflozin PSD, November 2020 PBAC meeting). This may be reasonable.
Proportion of heart failure patients treated with standard care	86.5%. Based on 2018-2019 (financial year) data from the 10% PBS longitudinal sample analysis	This estimate was considered uncertain. Averaging the monthly 10% sample data from July 2018 to August 2020 increased the estimated proportion to 90.1%.
Proportion of patients treated with standard care who have T2D	33.3%. Based on 2015-2020 data from the 10% PBS longitudinal sample analysis	Based on patients receiving one or more dispensed T2D medicines. May include patients not continuing treatment. The PSCR argued that patients who discontinue due to clinical issues are likely to switch therapy rather than cease treatment entirely. It also argued the estimate was reasonable in the context of a multimorbid population with a high prevalence of cardiometabolic disease.
Proportion of T2D and HFrEF treated with SGLT2i	10.6-13.5% over 6 years. Based on moving averages forecast derived from Jan 2014-Aug 2020 in the 10% PBS longitudinal sample analysis	Given use of SGLT2i in T2D may be impacted by heart failure trial outcomes, the estimate is uncertain.
Impact factor for increase in use of SGLT2i for T2D to account for increased prescribing of empagliflozin related to favourable cardiovascular outcomes in recent clinical trials	■-■% over 6 years. Assumed	The DUSC considered that SGLT2i uptake may increase due to known cardiovascular benefits (para 6.60, dapagliflozin, PSD, November 2020 PBAC meeting). This submission included an additional assumed uptake factor.
Uptake of SGLT2i for HFrEF	■-■% over 6 years. Assumed	Estimated uptake was substantially higher than estimated for dapagliflozin in the November 2020 submission (5-42%).
Empagliflozin adherence	95.1%. Based on post hoc descriptive analysis of the EMPEROR-Reduced trial. Used to calculate 11.58 scripts per patient per year.	The post hoc analysis could not be evaluated. Given trial adherence may not be realised in clinical practice, adherence is most likely overestimated.

Source: Table 4.1, pp215-216 of the submission

LVEF, left ventricular ejection fraction; PSD, public summary document; NYHA, New York Heart Association; T2D, type 2 diabetes; HFrEF, Heart failure with reduced ejection fraction; SGLT2i, sodium glucose co-transporter 2 inhibitor

6.73 The table below summarises the estimated net cost to the PBS/RPBS of listing empagliflozin for HFrEF, with the requested DPMQ of \$60.04 updated to include the July 2021 fee increases (DPMQ of \$60.10).

**Table 16: Estimated use and financial implications**

Estimated populations	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	
A Australian adults	20,757,917	21,082,471	21,411,852	21,744,502	22,073,220	22,393,101	
B Adults with HF (A×2.199%)	456,467	463,604	470,847	478,162	485,390	492,424	
C LVEF ≤40% (B×60%)	273,880	278,162	282,508	286,897	291,234	295,455	
D NYHA class II-IV (C×95%)	260,186	264,254	268,383	272,552	276,672	280,682	
E Eligible on standard care (D×86.5%)	225,118	228,638	232,210	235,817	239,382	242,851	
F HF patients without T2D (E×66.7%)	150,079	152,425	154,807	157,212	159,588	161,901	
G HF patients with T2D not treated with SGLT2i <sup>a</sup>	66,710	66,752	66,785	66,802	66,782	66,161	
H Prevalent patients (F+G)	216,788	219,177	221,591	224,014	226,370	228,062	
I Uptake rate (%)							
J Empagliflozin patients (H×I)							
K Total scripts PBS/RPBS (J×11.58/patient/year)							
L PBS/RPBS cost (K×\$60.10)							
M Patient copayment (K×\$13.10)							
N <b>Net cost to the PBS/RPBS</b>							

Source: Source: Table 4.2, p216; Table 4.4, p220; Tables 4.5 and 4.6, p221; Table 4.9, p223; Tables 4.10 and 4.11, p224; Tables 4.12 and 4.13, p225; Tables 4.14, 4.15, and 4.16, pp226-227 of the submission

<sup>a</sup> Based on the proportion of HF patients with type 2 diabetes who are not currently treated with an SGLT2i. Includes market growth estimates (■% increase in uptake) to account for increased prescribing of empagliflozin related to favourable cardiovascular outcomes in recent clinical trials.

The redacted values correspond to the following ranges:

- <sup>1</sup> 30,000 to < 40,000
- <sup>2</sup> 60,000 to < 70,000
- <sup>3</sup> 100,000 to < 200,000
- <sup>4</sup> 200,000 to < 300,000
- <sup>5</sup> 300,000 to < 400,000
- <sup>6</sup> 700,000 to < 800,000
- <sup>7</sup> 1,000,000 to < 2,000,000
- <sup>8</sup> 2,000,000 to < 3,000,000
- <sup>9</sup> \$20 million to < \$30 million
- <sup>10</sup> \$40 million to < \$50 million
- <sup>11</sup> \$70 million to < \$80 million
- <sup>12</sup> \$100 million to < \$200 million
- <sup>13</sup> \$0 to < \$10 million
- <sup>14</sup> \$10 million to < \$20 million
- <sup>15</sup> \$30 million to < \$40 million
- <sup>16</sup> \$60 million to < \$70 million

6.74 The submission estimated the net cost to the PBS/RPBS of listing empagliflozin on the PBS/RPBS for HFrEF at \$20 million to < \$30 million in Year 1, increasing to \$100 million to < \$200 million in Year 6, an estimated net cost of \$400 million to < \$500 million over the first six years of listing.

6.75 The estimated use and financial implications to the RPBS/PBS of listing empagliflozin for the treatment of HFrEF were uncertain for the following reasons:

- The risk of empagliflozin use outside the requested restriction is high. Empagliflozin is well known to prescribers and has demonstrated positive outcomes for cardiovascular disease, and heart failure with reduced or preserved ejection fraction.

- The proportion of patients with HFrEF and NYHA class II-IV symptoms treated with standard care (86.5%), based on July 2018-August 2019 data in the 10% PBS sample analysis, may have underestimated the eligible population, as a higher proportion (90.1%) was obtained when including more recent data (July 2018-August 2020).
- The submission inflated the expected use of SGLT2i medicines in the type 2 diabetes population to account for patients switching to SGLT2i from other medicines or non-pharmacological management in response to the cardiovascular and renal benefits of SGLT2i medicines demonstrated in recent clinical trials. The evaluation considered that this was reasonable, but the magnitude of the inflation factor was an assumption and the net impact of the proposed listing on the HFrEF and type 2 diabetes markets was uncertain.
- Estimated uptake of empagliflozin was considered to be high.
- Treatment adherence to empagliflozin of 95.1%, derived from a *post hoc* analysis of the EMPEROR-Reduced trial data, is unlikely to be realised in clinical practice, and may have overestimated the utilisation of empagliflozin in the eligible population.

### **Quality Use of Medicines**

- 6.76 The sponsor acknowledged the quality use of medicines concerns raised by the PBAC, the DUSC and the evaluation in the November 2020 consideration of dapagliflozin for the treatment of HFrEF (para 6.63, dapagliflozin, PSD, November 2020 PBAC meeting), and proposed a series of Quality Use of Medicine initiatives (face-to-face interactions, digital content and print materials) for patients and healthcare professionals, with a focus on clinicians, pharmacists and practice nurses.

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

- 6.77 No Risk Sharing Arrangement (RSA) was proposed. The ESC noted that the PBAC had recommended listing dapagliflozin for HFrEF, and that the estimates were broadly reasonable and would form an appropriate basis for an RSA to manage the risk of use outside the PBS restriction (PBAC Outcomes, September 2021 Intracycle meeting). The pre-PBAC response stated that the sponsor would accept a risk sharing arrangement for the HFrEF indication subject to approval of the subsidisation caps by its parent company.

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

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the listing of empagliflozin for the treatment of patients with chronic heart failure with reduced ejection fraction (HFrEF), New York Heart Association classification II-IV, left ventricular ejection fraction (LVEF)  $\leq 40\%$ , who are receiving standard care including a beta blocker, and an angiotensin-converting enzyme inhibitor (ACEi), or an angiotensin II receptor blocker (ARB), or an angiotensin receptor with neprilysin inhibitor (ARNi). Although the submission presented a

modelled economic evaluation against standard care, the PBAC's recommendation for listing was based on its assessment that the cost-effectiveness of empagliflozin would be acceptable if it were cost-minimised against dapagliflozin, which was recommended for listing of this indication at the PBAC's September 2021 Intracycle meeting.

- 7.2 The PBAC considered that the equi-effective doses were empagliflozin 10 mg per day and dapagliflozin 10 mg per day.
- 7.3 The PBAC considered that the PBS listing should align with the recommended listing for dapagliflozin (finalised wording shown in Section 8 below). The PBAC recommended that the listing should be silent on titration requirements for concomitant beta-blocker/ACEi/ARNi/ARB use, as this would be more in line with current clinical guidelines and expected practice.
- 7.4 The PBAC noted that the submission's main comparator of optimised standard care was aligned with the comparator it had considered reasonable for dapagliflozin for HFrEF (para 7.3, dapagliflozin PSD, July 2021 PBAC meeting). However, as dapagliflozin had since been recommended for this indication at the September 2021 PBAC meeting, and agreement to listing arrangements had been finalised at time of consideration (see Medicine Status Website), the PBAC considered that the submission's near-market comparison with dapagliflozin was the most relevant for decision making.
- 7.5 As with dapagliflozin, the PBAC held the view that the clinical place of SGLT2 inhibitors for heart failure was likely to continue to evolve. The PBAC noted that the European Society of Cardiology had recently updated its' *Guidelines for the diagnosis and treatment of acute and chronic heart failure* positioning dapagliflozin and empagliflozin as standard therapy for all patients already treated with an ACEi/ARNi, beta-blocker, and an MRA, regardless of whether they have diabetes or not.
- 7.6 In terms of the trial evidence presented, the PBAC recognised that the evaluation had raised concerns about the applicability of the EMPEROR-Reduced trial to the Australian setting, given differences with the Australian population for risk factors of age, sex, BMI as well as significant treatment effect interactions associated with baseline LVEF and race subgroups. However, the PBAC agreed with the ESC that these analyses should be regarded as exploratory only. For the indirect treatment comparison (ITC), the PBAC noted that both the empagliflozin trial (EMPEROR-Reduced) and the dapagliflozin trial (DAPA-HF) had a low risk of bias. Although there were some differences between trials identified during the evaluation, the PBAC agreed with the ESC's assessment that the differences were bidirectional.
- 7.7 The PBAC considered that the noninferiority margin should be based on both clinical and statistical judgement. The PBAC noted the ESC's advice that there appears to be broad consensus that the benefits for the SGLT2 inhibitors in HFrEF are a class effect, and that this is reflected in clinical guidelines and practice. The PBAC noted that this advice was further supported by the clinician presentation at the sponsor hearing. As

such, the PBAC agreed with the ESC that the claim of noninferior comparative effectiveness with dapagliflozin was reasonable.

- 7.8 In terms of comparative safety, the PBAC noted the summary of the key adverse events in the EMPEROR-Reduced trial, and the ITC with DAPA-HF for adverse events of interest. The PBAC considered that claim of noninferiority with dapagliflozin was reasonable, and consistent with the long experience in clinical practice for this class of medicines.
- 7.9 Ultimately, as stated above, the PBAC considered that the comparison to dapagliflozin was the most relevant and that the listing of empagliflozin would be cost-effective if cost-minimised to dapagliflozin for this indication (with equi-effective doses noted in paragraph 7.2).
- 7.10 The PBAC advised it would be appropriate for empagliflozin to be subject to the same Risk-Sharing Arrangement (RSA) subsidisation caps as for dapagliflozin for HFrEF. The PBAC considered that as empagliflozin would be subject to the same RSA as dapagliflozin, there would be no additional cost to the Commonwealth from the listing.
- 7.11 The PBAC advised that empagliflozin for HFrEF is suitable for prescribing by nurse practitioners for continuing therapy only.
- 7.12 The PBAC recommended that the Early Supply Rule should apply.
- 7.13 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because empagliflozin is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over dapagliflozin, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.
- 7.14 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## **8 Recommended listing**

- 8.1 Amend existing listing as follows:

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
EMPAGLIFOZIN					
empagliflozin 10 mg tablet, 30	NEW	1	30	5	Jardiance
<b>Restriction Summary [new] / Treatment of Concept: [new]</b>					
	<b>Category / Program:</b> GENERAL – General Schedule (Code GE)				
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners				
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (STREAMLINED) [new code]				
	<b>Indication:</b> Chronic heart failure				
	<b>Treatment Phase:</b> [blank]				
	<b>Clinical criteria:</b>				
	Patient must be symptomatic with NYHA classes II, III or IV,				
	<b>AND</b>				
	<b>Clinical criteria:</b>				
	Patient must have a documented left ventricular ejection fraction (LVEF) of less than or equal to 40%,				
	<b>AND</b>				
	<b>Clinical criteria:</b>				
	The treatment must be an add-on therapy to optimal standard chronic heart failure treatment, which must include a beta-blocker, unless contraindicated according to the TGA-approved Product Information or cannot be tolerated;				
	<b>AND</b>				
	<b>Clinical criteria:</b>				
	The treatment must be an add-on therapy to optimal standard chronic heart failure treatment, which must include an ACE inhibitor, unless contraindicated according to the TGA-approved Product Information or cannot be tolerated; or				
	The treatment must be an add-on therapy to optimal standard chronic heart failure treatment, which must include an angiotensin II antagonist, unless contraindicated according to the TGA-approved Product Information or cannot be tolerated; or				
	The treatment must be an add-on therapy to optimal standard chronic heart failure treatment, which must include an angiotensin receptor with neprilysin inhibitor combination therapy unless contraindicated according to the TGA-approved Product Information or cannot be tolerated,				
	<b>AND</b>				
	<b>Clinical criteria:</b>				
	Patient must not be receiving treatment with another sodium-glucose co-transporter 2 (SGLT2) inhibitor				
	<b>Administrative Advice:</b> Continuing Therapy Only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.				
	<b>Administrative advice:</b> No increase in the maximum quantity or number of units may be authorised.				
	<b>Administrative advice:</b> No increase in the maximum number of repeats may be authorised.				

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

## **9 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **10 Sponsor's Comment**

The sponsor had no comment.