6.01 DAPAGLIFLOZIN, Tablet 10 mg, Forxiga®, AstraZeneca Pty Ltd.

1 Purpose of submission

1.1 The submission requested an Authority Required (Streamlined) general schedule listing of dapagliflozin for the treatment of patients with chronic heart failure with reduced ejection fraction.

1.2 Listing was requested on the basis of a cost-minimisation analysis versus sacubitril/valsartan.

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

Component	Description
Population	Patients with symptomatic (NYHA class II-IV) chronic heart failure with reduced ejection fraction who are receiving (unless contraindicated or not tolerated) an ACE inhibitor, ARB or sacubitril/valsartan; a beta-blocker; and, if appropriate, an MRA.
Intervention	Dapagliflozin 10 mg once daily added to standard care comprising an ACE inhibitor, ARB or sacubitril/valsartan; a beta-blocker; and, if appropriate, an MRA.
Comparator	• Sacubitril/valsartan added to standard care comprising a beta-blocker and, if appropriate, an MRA. • Standard care alone comprising an ACE inhibitor, ARB or sacubitril/valsartan; a beta-blocker; and, if appropriate, an MRA.
Outcomes	Time to hospitalisation for heart failure; time to urgent heart failure visit; time to cardiovascular death; death; time to death from any cause; heart failure-related quality of life; safety.
Clinical claim	• When used in the management of patients with heart failure with reduced ejection fraction, dapagliflozin added to standard care (comprising an ACE inhibitor or ARB, a beta-blocker, and, if appropriate, an MRA), is non-inferior, in terms of effectiveness and safety, compared to sacubitril/valsartan added to standard care (comprising a beta-blocker; and, if appropriate, an MRA). • When used in the management of patients with heart failure with reduced ejection fraction, dapagliflozin added to standard care (comprising an ACE inhibitor, ARB, or sacubitril/valsartan; a beta-blocker; and, if appropriate, an MRA), is superior in terms of effectiveness to standard care alone (comprising an ACE inhibitor, ARB, or sacubitril/valsartan; a beta-blocker; and, if appropriate, an MRA). The submission did not make an explicit safety claim.

Source: Table 1.1-1 of the submission.
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

1.3 The submission defined standard care in the clinical claim as comprising an angiotensin-converting enzyme (ACE) inhibitor / angiotensin II receptor blocker (ARB) / sacubitril/valsartan; together with a beta-blocker; and, if appropriate, a mineralocorticoid receptor antagonist (MRA). While this was consistent with the inclusion criteria for the DAPA-HF trial, patients in the trial also continued other background heart failure treatments, such as digoxin, ivabradine, vasodilators, and diuretics. Therefore, background heart failure treatments (referred to as standard care) incorporated a broader range of treatments than defined in the clinical claim.

However, the ESC felt that the impact of these other therapies on outcomes and costs was likely to be minimal and likely to be similar on both sides.

2 Background

Registration status

2.1 **TGA status at the time of PBAC consideration:** the submission was made under the TGA/PBAC parallel process. At the time of the PBAC consideration, the TGA Round 1 clinical evaluation report and the Delegate's Overview were available.

2.2 The sponsor's proposed TGA indication for dapagliflozin was:

> Dapagliflozin is indicated in adults for the treatment of heart failure with reduced ejection fraction.

2.3 The TGA delegate noted that the DAPA-HF trial did not establish, nor was it designed to establish, that dapagliflozin monotherapy has a place in the treatment of heart failure, and proposed that the proposed heart failure indication be amended as follows:

> Dapagliflozin is indicated in adults for the treatment of symptomatic heart failure with reduced ejection fraction, as an adjunct to standard of care therapy.

2.4 The TGA delegate considered that while the efficacy of dapagliflozin in the treatment of patients with NYHA Class II HFrEF has been satisfactorily established, the evidence in the more severe Class III and IV patients is somewhat equivocal. Study participants with Class IV heart failure represented only around 1% of the study population and in the pre-defined statistical analysis by subgroups, the Class III and Class IV groups were combined. While the hazard ratio for the combined group and indeed for the separate groups indicated a possible benefit for dapagliflozin, the 95% CI crossed unity in each case.

2.5 The TGA delegate noted that the median duration of follow-up time for patients in DAPA-HF trial was around 18 months. At the data lock point, only around 10% of the study population had been exposed to treatment for two years or more. While the event-driven efficacy endpoint was achieved, the period of exposure may have been too short to unveil any rare or unusual long-term safety issues. However, the ESC noted that dapagliflozin has been widely used in clinical practice in the Type 2 diabetes mellitus (T2DM) population and that longer term safety data in this population is available.

2.6 Dapagliflozin was registered by the TGA for use in T2DM on 22 October 2012, and is currently registered for the following indications in adults with Type 2 diabetes:

- As monotherapy as an adjunct to diet and exercise in patients for whom metformin is otherwise indicated but was not tolerated.

- As initial combination therapy with metformin, as an adjunct to diet and exercise, to improve glycaemic control when diet and exercise have failed to provide adequate glycaemic control and there are poor prospects for response to metformin monotherapy (for example, high initial haemoglobin A1c [HbA1c] levels).
- In combination with other anti-hyperglycaemic agents to improve glycaemic control, when these together with diet and exercise, do not provide adequate glycaemic control.

2.7 Dapagliflozin is also registered for use in adults with T2DM and established cardiovascular disease or risk factors for cardiovascular disease to reduce the risk of hospitalisation for heart failure.

2.8 Dapagliflozin is currently PBS listed for the treatment of T2DM as dual therapy with metformin, a sulfonylurea or insulin, and as triple therapy with metformin plus a sulfonylurea or metformin plus a dipeptidyl peptidase 4 inhibitor (gliptin).

2.9 The ESC noted that the PBAC (paragraph 7.9, liraglutide, Public Summary Document, July 2017), has previously recognised that PBS subsidised diabetes medications have been recommended on the basis of an assumed reduction in CV events and the current price of diabetes medications, including dapagliflozin, incorporates this assumed benefit. The ESC felt that there was a risk that the Australian Government would end up paying more for the heart failure indication than it does currently in the overlapping T2DM population.

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

3 Requested listing

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

Name, Restriction, Manner of administration and form	Max. Qty (packs)	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
DAPAGLIFLOZIN Tablets 10 mg, 28	1	5	$[redacted]	Forxiga® AstraZeneca Australia Pty Ltd

Category/Program:	GENERAL – General Schedule (Code GE)
PBS indication:	~~Heart failure with reduced ejection fraction~~ *Chronic heart failure*
~~Treatment phase:~~	~~Initial and continuing~~
Restriction:	Authority Required (Streamlined)
Clinical criteria:	Patient must be symptomatic with *NYHA* ~~New York Heart Association~~ classes II, III or IV, AND Patient must have a documented left ventricular ejection fraction *(LVEF)* of less than or equal to 40%, AND Patient must receive concomitant optimal standard chronic heart failure treatment, which must include~~:~~ *the maximum tolerated dose of a beta-blocker, unless contraindicated or not tolerated;* *AND* *Patient must be receiving treatment with an ACE inhibitor, unless contraindicated according to the TGA-approved Product Information or cannot not be tolerated; or* *Patient must be receiving treatment with an angiotensin II antagonist, unless contraindicated according to the TGA-approved Product Information or cannot not 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 not be tolerated,* ~~EITHER an angiotensin converting enzyme inhibitor OR an angiotensin II antagonist OR an angiotensin receptor neprilysin inhibitor, unless contraindicated or not tolerated~~ ~~AND~~ ~~maximum tolerated dose of a beta-blocker, unless contraindicated or not tolerated,~~ AND ~~The treatment must not be co-administered with other sodium-glucose co-transporter-2 inhibitors.~~ *Patient must not be receiving treatment with another sodium-glucose co-transporter 2 (SGLT2) inhibitor.*
Administrative advice:	Note Continuing Therapy Only: For prescribing by Nurse Practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. *Further information can be found in the Explanatory Notes for Nurse Practitioners.*

3.2 The submission noted that sacubitril/valsartan is subject to a special pricing arrangement, and that the price of dapagliflozin would need to be calculated based on the results of the cost-minimisation analysis using the sacubitril/valsartan effective price.

3.3 The proposed published DPMQ is higher than the dapagliflozin DPMQ for the T2DM indication. The submission requested a revised published price for dapagliflozin to reflect the proportional use across heart failure and diabetes indications. The pre-PBAC response proposed that the price in T2DM remain as it is currently and that the price in heart failure be calculated as: [redacted]% at the current T2DM price (comorbid Type 2 diabetes patients ([redacted]%) and concomitant sacubitril/valsartan patients ([redacted]%)) and [redacted]% at the requested price in HFrEF (cost-minimisation to sacubitril/valsartan minus cost of valsartan). The pre-PBAC response then proposed that the new dapagliflozin

price be weighted across the heart failure price and the T2DM price, based on estimated utilisation at [redacted]% and [redacted]% respectively. The PBAC did not accept the new price offer as the cost-effectiveness of dapagliflozin compared to standard care was not established (see Section 7 PBAC outcome).

3.4 The proposed restriction is narrower than the indication in the draft product information, which does not restrict treatment on the basis of heart failure severity (NYHA class), left ventricular ejection fraction, or concomitant heart failure therapies. The proposed restriction is consistent with the DAPA-HF trial, which recruited patients with NYHA Class II-IV heart failure, a left ventricular ejection fraction (LVEF) ≤40%, and who were optimised on an ACE inhibitor, ARB, or sacubitril/valsartan; and a beta blocker. However, the inclusion criteria for the DAPA-HF trial also required patients to be treated with an MRA if considered appropriate by the patient's treating physician.

3.5 The proposed restriction allows use of dapagliflozin in combination with an angiotensin receptor neprilysin inhibitor (ARNI; i.e. sacubitril/valsartan). Given that dapagliflozin has a different mechanism of action compared to sacubitril/valsartan, patients requiring intensification of treatment may use dapagliflozin in combination with sacubitril/valsartan, rather than substitute for it. The PBAC noted the cost-effectiveness of dapagliflozin as an add-on to sacubitril/valsartan was not examined in this submission.

3.6 There is potential for use outside of the requested restriction among patients with heart failure preserved ejection fraction (HFpEF), patients with NYHA Class I heart failure, and among patients who are not on optimised therapy with an ACE inhibitor/ARB and beta blocker.

3.7 The requested clinical criteria are consistent with the sacubitril/valsartan restriction in terms of NYHA class (II-IV), a documented LVEF ≤40%, and the requirement for optimised heart failure treatment with the maximum dose of a beta-blocker (unless contraindicated or not tolerated). Patients treated with sacubitril/valsartan must be stabilised on an ACE inhibitor or ARB (unless contraindicated or not tolerated) prior to sacubitril/valsartan initiation, but do not require treatment with an MRA.

3.8 A submission for sacubitril/valsartan was considered at the November 2020 PBAC meeting. That submission requested changes to the current sacubitril/valsartan chronic heart failure listing to include a broader population of patients.

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

4 Population and disease

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

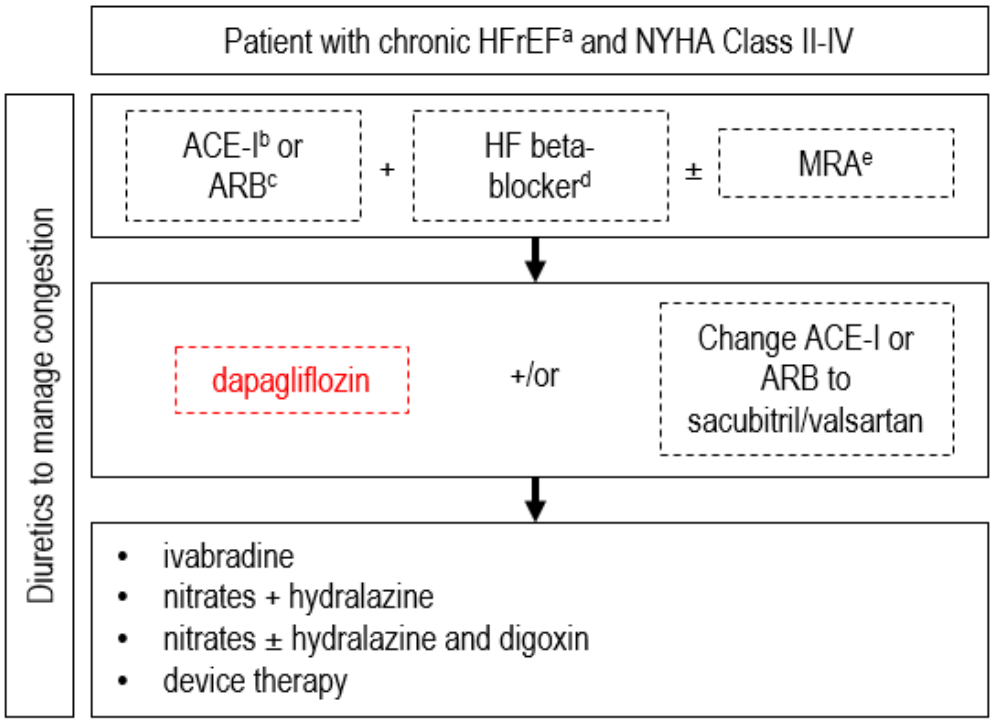
4.2 It was estimated that there were 480,000 people aged 18 years or more in Australia with heart failure in 2014, representing 2.1% of the adult population. The age-standardised prevalence rates of heart failure in Indigenous Australians is estimated to be 1.7 times higher than in non-Indigenous Australians (Woods et al, 2012). The risk of death in symptomatic heart failure is high, with a 20-30% one-year mortality in mild to moderate HF and over 50% one-year mortality in severe heart failure, rising with each rehospitalisation (Carson et al, 2015).

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

4.4 Acute episodes of decompensation requiring hospitalisation are relatively common, with around a third of patients with heart failure hospitalised each year (Krum et al., 2011). Common reasons for hospitalisation with acute heart failure are infection, non-adherence to medication, and non-adherence to dietary and fluid restrictions. Heart failure is primarily managed by the general practitioner, with specialist input as required (e.g. at times of decompensation). Comprehensive multidisciplinary programs have an increasingly important role in patient education and treatment supervision.

4.5 Figure 1 below presents the proposed clinical management algorithm presented in the submission.

Figure 1: Proposed clinical algorithm for patients with heart failure and reduced ejection fraction



Source: Figure 1.2-2, p.31 of the submission.
Abbreviations: ACE-I, Angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.
[a] HFrEF refers to patients with symptoms ± signs of HF associated with an LVEF less than 50%.
[b] PBS-listed ACE inhibitors include ramipril, enalapril, fosinopril, lisinopril, quinapril, captopril, trandolapril.
[c] PBS-listed ARBs include irbesartan, candesartan, telmisartan, valsartan, olmesartan, eprosartan, losartan and should only be used if an ACE inhibitor is contraindicated.
[d] PBS-listed HF beta-blockers include bisoprolol, carvedilol, metoprolol extended release, nebivolol.
[e] PBS-listed MRAs include spironolactone, eplerenone.

4.6 The submission positioned dapagliflozin as an alternative or add-on option to sacubitril/valsartan when intensification of treatment is required following stabilisation on therapy with an ACE inhibitor/ARB, a beta-blocker and a MRA. The ESC noted that approximately 11% of patients in the pivotal trial used both dapagliflozin and sacubitril/valsartan and the pre-sub-committee response (PSCR) suggested concomitant use of dapagliflozin and sacubitril/valsartan in the Australian clinical setting is likely to remain low, approximately less than 20%. The ESC also considered dapagliflozin might displace sacubitril/valsartan, which has had a low uptake since PBS listing, and potentially grow the market for heart failure where sacubitril/valsartan is not being used.

4.7 The National Heart Foundation guidelines (2018) do not contain specific recommendations for the use of SGLT2 inhibitors in the treatment of established heart failure. SGLT2 inhibitors are recommended in patients with T2DM associated with cardiovascular disease and insufficient glycaemic control despite metformin, to decrease the risk of cardiovascular events and decrease the risk of hospitalisation for heart failure.

4.8 The PBAC considered the positioning of dapagliflozin (and other SGLT2-inhibitors) was unclear and likely to evolve. Sacubitril/valsartan and dapagliflozin have different optimal patient profiles and dapagliflozin was more likely to be used in patients with diabetes, normotension/relative hypotension or fluid overload, whereas sacubitril/valsartan may be preferred for use in patients with hypertension.

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

5 Comparator

5.1 The submission nominated sacubitril/valsartan plus standard care as the main comparator. The main arguments provided in support of this nomination were:

- Sacubitril/valsartan is currently PBS-listed for the treatment of patients with heart failure with reduced ejection fraction (HFrEF) who need intensification of therapy despite use of optimal standard heart failure treatment, including an ACE inhibitor or ARB, and the maximum tolerated dose of a beta-blocker (unless contraindicated or not tolerated).
- Sacubitril/valsartan is the medication with the greatest extent of use at the point where dapagliflozin is introduced into the management algorithm. In the key clinical trial (DAPA-HF), the majority of use of dapagliflozin (approximately 65%) occurred following treatment with an ACE inhibitor or ARB or sacubitril/valsartan, a beta blocker, and an MRA. This argument may not be reasonable given that treatment with an ACE inhibitor (or ARB or ARNI), a beta blocker, and an MRA (unless contraindicated or not tolerated) formed part of the inclusion criteria for the trial. Patients in the DAPA-HF trial also continued other background heart failure treatments, including diuretics, digoxin, ivabradine and vasodilators.
- Feedback from clinicians suggests that when intensifying treatment following treatment with an ACE inhibitor/ARB, a beta blocker, and an MRA, the choice would generally be made between sacubitril/valsartan and dapagliflozin. The proposed restriction does not require treatment with an MRA prior to initiation of dapagliflozin, although this is the same as the sacubitril/valsartan PBS listing.

5.2 The evaluation considered sacubitril/valsartan plus standard care may not be the appropriate <u>main</u> comparator due to the following reasons:

- Based on the financial estimates presented in Section 4 of the submission, the majority of patients expected to use dapagliflozin are derived through broadening of the heart failure market rather than substitution for sacubitril/valsartan.
- The proposed restriction allows treatment with dapagliflozin in combination with sacubitril/valsartan. Given that dapagliflozin has a different mechanism of action compared to sacubitril/valsartan, patients already receiving sacubitril/valsartan who require intensification of therapy are likely to add dapagliflozin to their current therapy rather than substituting for sacubitril/valsartan (and then having to reinstitute therapy with an ACE inhibitor or ARB). Patients who receive

treatment with dapagliflozin in preference to sacubitril/valsartan may well add sacubitril/valsartan on top of dapagliflozin at a later time.

5.3 The ESC considered that the addition of dapagliflozin may result in important changes to standard care and the positioning of other drugs such as diuretics in the clinical management algorithm. Given dapagliflozin's substantial diuretic effect, it may be necessary to cease treatment with an MRA, a class of drugs that not only provides symptomatic relief to patients but also offers prognostic value in the treatment of heart failure.

5.4 The submission also nominated standard care as a minor comparator based on the following considerations:

- Dapagliflozin is expected to broaden the heart failure patient population who receive the clinical benefits of intensified treatment following use of an ACE inhibitor or ARB, beta blocker, and an MRA.
- The submission claimed that clinicians have confirmed that, although the clinical need for treatment intensification after use of an ACE inhibitor or ARB, beta blocker, and an MRA remains, sacubitril/valsartan is a difficult to manage medication due to the initiation, up-titration and monitoring requirements, as well as the impacts it poses on adjustment of background standard care heart failure therapies.

5.5 The PBAC agreed with the ESC that standard care should be the main comparator. Based on the proposed treatment algorithm, standard care would include initial treatment with an ACE inhibitor (or ARB), a beta blocker and an MRA (if tolerated and not contraindicated), along with additional heart failure therapies such as sacubitril/valsartan, ivabradine, nitrates plus hydralazine, digoxin, and device therapy (implantable cardioverter defibrillator or cardiac resynchronisation therapy) as required. Standard care also includes the use of diuretics at any stage to manage congestion. The ESC noted standard care is variable.

5.6 The ESC noted a majority of patients (approximately 89%) in the DAPA-HF trial were not using an ARNI as part of standard care and considered this would likely reflect Australian clinical practice. Therefore, the majority of dapagliflozin use will not be replacing sacubitril/valsartan and the most relevant comparator for PBAC consideration would be standard care, consisting of a beta blocker, plus an ACE inhibitor or ARB. The PBAC considered that its previous recommendation for sacubitril/valsartan was not an appropriate proxy for standard care for this dapagliflozin submission.

5.7 The PBAC agreed with the ESC that an additional minor comparator would be beta blocker plus ARNI.

5.8 The submission noted that other SGLT2 inhibitors may be potential near-market comparators, but argued that results for trials of alternative SGLT2 inhibitors in heart failure were not currently available. The results of a Phase 3 randomised, double-blind

trial to evaluate efficacy and safety of empagliflozin compared to placebo, in patients with chronic heart failure with reduced ejection fraction (EMPEROR-Reduced) were published in August 2020 (Packer et al. 2020). The trial met its primary endpoint, demonstrating superiority compared to placebo in reducing the risk for the composite of cardiovascular death or hospitalisation due to heart failure, when added to standard of care. The ESC noted the published hazard ratio for this outcome was similar to that seen with dapagliflozin in DAPA-HF, but no formal analysis has been undertaken.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The submission was based on the following comparisons of dapagliflozin and the nominated comparators:

- A head-to-head comparison of dapagliflozin plus standard care versus placebo plus standard care in patients with NYHA Class II-IV heart failure with reduced ejection fraction (DAPA-HF trial).
- An indirect comparison of dapagliflozin plus standard care (DAPA-HF trial full population) versus sacubitril/valsartan plus standard care (PARADIGM-HF trial), using placebo plus standard care (DAPA-HF trial full population) and enalapril plus standard care (PARADIGM-HF) as common reference.
- An indirect comparison and an anchored MAIC of dapagliflozin plus standard care including an ACE inhibitor or ARB (subgroup of the DAPA-HF dapagliflozin arm) versus sacubitril/valsartan plus standard care (PARADIGM-HF trial), using placebo plus standard care including an ACE inhibitor (subgroup of the DAPA-HF placebo arm) and enalapril plus standard care (PARADIGM-HF) as common reference.

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

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
DAPA-HF	Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF).	Clinical Study Report, October 2019.
	McMurray JJV, DeMets DL, Inzucchi SE, et al. The Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) trial: baseline characteristics.	*European Journal of Heart Failure* 2019; 21(11): 1402-1411.
	McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction.	*New England Journal of Medicine* 2019; 381(21): 1995-2008.
	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).	*European Journal of Heart Failure* 2019; 21(5): 665-675.
PARADIGM-HF	McMurray JJV, Packer M, Desai AS, et al. Baseline characteristics and treatment of patients in Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in heart failure trial (PARADIGM-HF).	*European Journal of Heart Failure* 2014; 16(7): 817-825.
	McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure.	*New England Journal of Medicine* 2014; 371(11): 993-1004.
	McMurray JJV, Packer M, Desai AS, et al. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: Rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF).	*European Journal of Heart Failure* 2013; 15(9):1062-73.
	Rizkala AR, Shi V, Chang WH, et al. A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic heart failure and reduced ejection fraction.	Novartis Clinical Study Protocol CLCZ696B2314. V01, Sep 2009

Source: Table 2.2-1, pp42-43 of the submission.

6.5 The key features of the included trials are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Dapagliflozin + standard care vs placebo + standard care					
DAPA-HF	4744	Phase 3, multi-centre, parallel-group, randomised, double-blind, placebo-controlled study (median duration of follow-up 18 months)	Low	• Age ≥18 years with symptomatic HFrEF • LVEF ≤40% • NYHA Class II-IV HF • NT-proBNP ≥600 pg/mL • On background therapy with an ACE inhibitor (or ARB or sacubitril/valsartan), a beta-blocker; and an MRA (if considered appropriate)	• Time to CV death, hospitalisation for HF, or urgent HF visit • Time to CV death or hospitalisation for HF • CV death or recurrent HF hospitalisations • Change in KCCQ-TSS • Time to ≥50% decline in eGFR, ESRD or renal death • Time to death from any cause
Sacubitril/valsartan + standard care vs enalapril + standard care					
PARADIGM-HF	8399	Phase 3, multi-centre, parallel-group, randomised, double-blind, active-controlled study (median duration of follow-up 27 months)	Low	• Age ≥18 years • LVEF ≤40%[1] • NYHA Class II-IV HF • Plasma BNP ≥150 pg/ml or NT-proBNP ≥600 pg/mL • On background therapy with an ACE inhibitor (or ARB), a beta-blocker; and an MRA (if considered appropriate)	• Time to CV death or hospitalisation for HF • Time to death from any cause • Change in KCCQ-CSS • Time to new-onset AF • Time to decline in renal function

Source: Section 2.3.1, pp45-48 of the submission; Table 2.5-3, p.77 of the submission; Attachment 2.4 of the submission; Table 2, p.1065 of McMurray et al. (2013).

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

[1] Changed from ≤40% to ≤35% in a protocol amendment that occurred during recruitment.

6.6 The DAPA-HF trial was an international, multi-centre trial conducted across 410 study sites in 20 countries in the Asia/Pacific (23%), Europe (45%), North America (14%) and South America (17%). Patients were randomised to receive dapagliflozin or placebo in addition to background heart failure treatments. The final clinical study report was available during the evaluation. The DAPA-HF trial had a low risk of bias.

6.7 The PARADIGM-HF trial was an international, multi-centre trial conducted across 1,043 study sites in 47 countries in the Asia/Pacific (18%), Central Europe (34%), Western Europe/Other (24%), Latin America (17%) and North America (7%). The PARADIGM-HF trial included a single-blind run-in phase in which patients received enalapril 10 mg twice daily for two weeks, followed by sacubitril/valsartan 48.6/51.4 mg for one to two weeks, then 97.2 mg/102.8 mg for two to four weeks. Only patients who tolerated both run-in periods entered the double-blind randomised treatment phase. Patients were randomised to receive sacubitril/valsartan or enalapril in addition to background heart failure treatments. The PARADIGM-HF trial had a low risk of bias.

6.8 The PARADIGM-HF trial was stopped early, according to pre-specified rules, after a median follow-up of 27 months, as the boundary for a benefit with sacubitril/valsartan had been crossed.

6.9 Baseline characteristics were generally well matched between treatment arms of the DAPA-HF and PARADIGM-HF trials. However, the inclusion of the PARADIGM-HF run-in phase may impact the exchangeability of the trial results in the indirect comparison.

6.10 Compared to the PARADIGM-HF trial, patients in the DAPA-HF trial were older (mean age 66.3 years versus 63.8 years), with a higher mean LVEF (31.1% versus 29.5%), and a higher proportion of diabetic patients (42% versus 35%). There were patients in PARADIGM-HF with NYHA Class I and none in DAPA-HF (5% versus 0% in DAPA-HF), there was a higher proportion of Class II (70% versus 68% in DAPA-HF), and a lower proportion with NYHA Class III (24% versus 32% in DAPA-HF).

6.11 There were differences in background heart failure therapies between the trials, with a higher proportion of patients in the DAPA-HF trial on a diuretic (93% versus 80%), a beta blocker (96% versus 93%), and an MRA (71% versus 56%) at baseline. A higher proportion of patients in the PARADIGM-HF trial were receiving treatment with digoxin (30% versus 19%). The ESC considered that these differences in patient characteristics and background treatments were relatively minor, appeared bidirectional and were unlikely to have significantly impacted outcomes.

6.12 At baseline, 56% of patients in DAPA-HF were receiving background treatment with an ACE inhibitor, 28% were receiving an ARB, and 11% of were receiving sacubitril/valsartan (patients in the PARADIGM-HF trial were switched to protocol specified sacubitril/valsartan or enalapril).

6.13 The submission proposed a non-inferiority margin of 1.104 for the composite outcome of time to cardiovascular death or hospitalisation for heart failure, based on the non-inferiority margin used in a trial comparing aliskiren monotherapy to enalapril monotherapy, in patients with heart failure with reduced ejection fraction (ATMOSPHERE study; Krum et al, 2011). The ESC considered this was reasonable.

6.14 The submission proposed a non-inferiority margin of 1.41 for the outcome of time to death from any cause, based on the non-inferiority margin used for the composite outcome of time to death from any cause, myocardial infarction and stroke in a study comparing percutaneous coronary intervention with drug-eluting stents to coronary artery bypass grafting, in patients with left main coronary artery disease (Stone et al., 2016). The ESC agreed with the evaluation that the choice of this non-inferiority margin and its applicability to the outcome of time to death from any cause among patients with heart failure with reduced ejection fraction is unclear and adequate justification for its use was not provided.

6.15 The submission proposed a non-inferiority margin of 1.33 for the outcome of time to cardiovascular death, based on the non-inferiority margin used for the composite outcome of cardiovascular death, myocardial infarction and stroke used in a study

comparing celecoxib, ibuprofen and naproxen, in patients requiring NSAIDs for osteoarthritis or rheumatoid arthritis who were at increased cardiovascular risk (PRECISION study; Nissen et al., 2016). The ESC agreed with the evaluation that the choice of this non-inferiority margin and its applicability to the outcome of time to cardiovascular death among patients with heart failure with reduced ejection fraction is unclear and adequate justification for its use was not provided.

Comparative effectiveness

6.16 Table 4 presents the results of the DAPA-HF trial based on the protocol-specified hierarchical testing sequence.

Table 4: Results for the DAPA-HF trial primary and secondary outcomes based on the hierarchical testing sequence

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

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

Source: Table 2.5-1, p.74 of the submission.

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

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

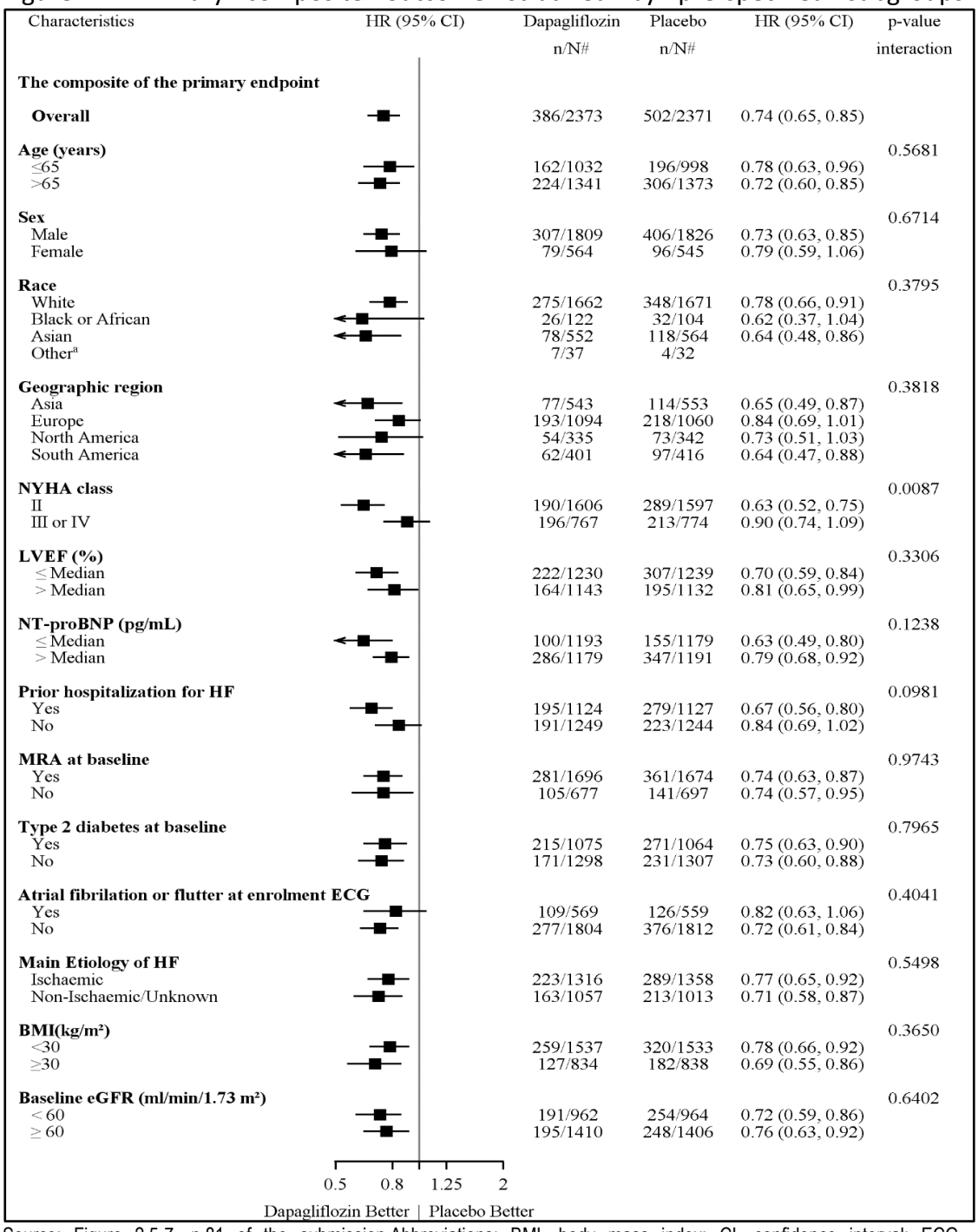
[2] Scored on a scale from 0 to 100, with a higher score indicating fewer symptoms and a change of 5 or more points considered to be clinically meaningful.

6.17 Treatment with dapagliflozin was associated with a statistically significant improvement in the primary composite endpoint of time to cardiovascular death, hospitalisation for heart failure or urgent heart failure visit compared to placebo (hazard ratio: 0.74; 95% CI: 0.65, 0.85), the composite of time to cardiovascular death or hospitalisation for heart failure (hazard ratio: 0.75; 95% CI: 0.65, 0.85), the composite of cardiovascular death or recurrent heart failure hospitalisation (rate ratio: 0.75; 95% CI: 0.65, 0.88), and the change in the Kansas City Cardiomyopathy Questionnaire (win ratio: 1.18; 95% CI: 1.11, 1.26). There was no statistically significant difference in the composite of time to ≥50% sustained decline in eGFR, end-stage renal disease or renal death (hazard ratio: 0.71; 95% CI: 0.44, 1.16). The hierarchical testing sequence stopped prior to the outcome of time to death from any cause being assessed.

6.18 The benefit of dapagliflozin on the composite of CV death or HF events was generally consistent across pre-specified subgroups, including patients without T2DM.

However, subgroup analysis suggested that dapagliflozin may be less effective in patients with NYHA Class III or IV heart failure (see Figure 2).

6.19 Figure 2: Primary composite outcome stratified by pre-specified subgroups



Source: Figure 2.5-7, p.81 of the submission.Abbreviations: BMI, body mass index; CI, confidence interval; ECG, electrocardiogram; GFR, glomerular filtration rate; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; MRA,mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association.

6.20 Table 5 presents the results of the indirect comparison of dapagliflozin plus standard care (DAPA-HF trial full population) versus sacubitril/valsartan plus standard care (PARADIGM-HF trial), using placebo plus standard care (DAPA-HF trial full population) and enalapril plus standard care (PARADIGM-HF) as common reference.

Table 5: Results of the indirect comparison based on the full DAPA-HF trial population

Trial	Dapagliflozin + SOC events n/N (%)	Common reference: Placebo + SOC/ enalapril + SOC events n/N (%)	Sacubitril/valsartan + SOC events n/N (%)	HR (95% CI)
Composite of time to cardiovascular death or hospitalisation for HF				
DAPA-HF (18 months)	382 / 2373 (16.1)	495 / 2371 (20.9)	-	0.75 (0.65, 0.85)
PARADIGM-HF (27 months)	-	1117 / 4212 (26.5)	914 / 4187 (21.8)	0.80 (0.73-0.87)
Indirect comparison of dapagliflozin + SOC vs. sacubitril/valsartan + SOC (proposed non-inferiority margin: 1.104)				**0.94 (0.80, 1.10)**
Time to hospitalisation for heart failure				
DAPA-HF (18 months)	231 / 2373 (9.7)	318 / 2371 (13.4)	-	0.70 (0.59, 0.83)
PARADIGM-HF (27 months)	-	658 / 4212 (15.6)	537 / 4187 (12.8)	0.79 (0.71, 0.89)
Indirect comparison of dapagliflozin + SOC vs. sacubitril/valsartan + SOC (no non-inferiority margin proposed)				**0.89 (0.72, 1.09)**
Time to cardiovascular death				
DAPA-HF (18 months)	227 / 2373 (9.6)	273 / 2371 (11.5)	-	0.82 (0.69, 0.98)
PARADIGM-HF (27 months)	-	693 / 4212 (16.5)	558 / 4187 (13.3)	0.80 (0.71, 0.89)
Indirect comparison of dapagliflozin + SOC vs. sacubitril/valsartan + SOC (proposed non-inferiority margin: 1.33)				**1.03 (0.83, 1.26)**
Time to death from any cause				
DAPA-HF (18 months)	276 / 2373 (11.6)	329 / 2371 (13.9)	-	0.83 (0.71, 0.97)
PARADIGM-HF (27 months)	-	835 / 4212 (19.8)	711 / 4187 (17.0)	0.84 (0.76, 0.93)
Indirect comparison of dapagliflozin + SOC vs. sacubitril/valsartan + SOC (proposed non-inferiority margin: 1.41)				**0.99 (0.82, 1.19)**

Source: Table 2.6-3, p.98 of the submission; Table 2, p.6 of McMurray et al. (2019); Table 2, p.999 of McMurray et al. (2014).
Abbreviations: CI, confidence interval; HF, heart failure; HR, hazard ratio, SOC, standard care.

6.21 There were no statistically significant differences between dapagliflozin and sacubitril/valsartan for the composite outcome of time to cardiovascular death or hospitalisation for heart failure, time to hospitalisation for heart failure, time to cardiovascular death, or time to death from any cause. The upper 95% confidence intervals were less than the nominated non-inferiority margins for the composite of time to cardiovascular death or hospitalisation for heart failure, time to cardiovascular death, and time to death from any cause comparisons. The applicability of the nominated non-inferiority margins for time to cardiovascular death and time to death from any cause was unclear, as they were not derived from trials in heart failure, and were based on composite (rather than single) outcomes.

6.22 The submission presented additional indirect analyses that were limited to a subgroup of patients in the placebo arm of DAPA-HF who were receiving treatment with an ACE inhibitor (to better match the enalapril arm of the PARADIGM-HF trial), and a subgroup of the dapagliflozin treatment arm receiving standard care that included an ACE inhibitor or ARB. The selection of post hoc subgroups from the DAPA-HF trial to more closely align with the patient population in PARADIGM-HF may have introduced bias into the comparisons.

6.23 Table 6 presents the results of the indirect comparison of dapagliflozin plus standard care including an ACE inhibitor or ARB (subgroup of the DAPA-HF dapagliflozin arm) versus sacubitril/valsartan plus standard care (PARADIGM-HF trial), using placebo plus standard care including an ACE inhibitor (subgroup of the DAPA-HF placebo arm) and enalapril plus standard care (PARADIGM-HF) as common reference.

Table 6: Results of indirect comparison based on the DAPA-HF trial subgroups

Outcome	DAPA-HF	PARADIGM-HF	Indirect comparison HR (95% CI)	Non-inferiority margin
	Dapagliflozin + SOC including ACE/ARB (n=1996) vs placebo + SOC including ACE (n=1329) HR (95% CI)	Sacubitril/valsartan + SOC (N=4187) vs enalapril + SOC (N=4212) HR (95% CI)		
Composite of time to CV death or hospitalisation for HF	0.73 (0.62, 0.86)	0.80 (0.73, 0.87)	0.92 (0.76, 1.10)	1.104
Time to hospitalisation for heart failure	0.73 (0.59, 0.91)	0.79 (0.71, 0.88)	0.93 (0.73, 1.18)	-
Time to cardiovascular death	0.71 (0.57, 0.87)	0.80 (0.71, 0.90)	0.89 (0.70, 1.12)	1.33
Time to death from any cause	0.75 (0.62, 0.91)	0.84 (0.76, 0.93)	0.89 (0.72, 1.11)	1.41

Source: Table 2.6-3, p.97 of the submission.
Abbreviations: ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; SOC, standard care.

6.24 There were no statistically significant differences between dapagliflozin and sacubitril/valsartan for the composite outcome of time to cardiovascular death or hospitalisation for heart failure, time to hospitalisation for heart failure, time to cardiovascular death, or time to death from any cause based on the subgroup analysis. Where nominated, the upper 95% confidence interval was less than the non-inferiority margin proposed in the submission.

6.25 Results of the indirect comparison should be interpreted with caution due to differences between the trials in eligibility criteria (LVEF cut-off), trial design (run-in periods), common reference arms (placebo plus standard care versus fixed dose enalapril plus standard care), patient characteristics (background therapies, heart failure severity, proportion of patients with diabetes), follow-up durations (18 months versus 27 months), and trial locations (20 countries versus 47 countries). The ESC considered that the common reference arms, which represent the 'anchor' may be acceptable if enalapril was representative of any ACE/ARB. The other differences were not considered major issues.

6.26 The submission also presented the results of an anchored MAIC of dapagliflozin plus standard care including an ACE inhibitor or ARB (subgroup of the DAPA-HF dapagliflozin arm) versus sacubitril/valsartan plus standard care (PARADIGM-HF trial), using placebo plus standard care including an ACE inhibitor (subgroup of the DAPA-HF placebo arm) and enalapril plus standard care (PARADIGM-HF) as common reference.

6.27 Matching for the selected variables resulted in a large reduction in sample size in the already reduced placebo plus standard care including an ACE inhibitor and dapagliflozin including an ACE inhibitor or ARB subgroups. There was limited documentation relating to the identification of treatment effect modifier variables and it was unclear whether all relevant treatment effect modifiers were matched in the analysis. In particular, differences in background heart failure therapies were not adjusted for in the analysis. The ESC considered the reduced sample was not a major issue if the common reference arms anchoring the MAIC were considered acceptable.

6.28 Summary results of the MAIC are presented in Table 7.

Table 7: Results of the matching adjusted indirect comparison (MAIC) based on the DAPA-HF trial subgroups

Outcome	DAPA-HF	PARADIGM-HF	MAIC HR (95% CI)	Non-inferiority margin
	Dapagliflozin + SOC including ACE/ARB (ESS=873) vs placebo + SOC including ACE (ESS=503) HR (95% CI)	Sacubitril/valsartan + SOC (N=4187) vs enalapril + SOC (N=4212) HR (95% CI)		
Composite of time to CV death or hospitalisation for HF	0.75 (0.58, 0.96)	0.80 (0.73, 0.87)	0.93 (0.71, 1.22)	1.104
Time to hospitalisation for heart failure	0.75 (0.56, 1.01)	0.79 (0.71, 0.88)	0.95 (0.69, 1.30)	-
Time to cardiovascular death	0.74 (0.53, 1.05)	0.80 (0.71, 0.90)	0.93 (0.64, 1.33)	1.33
Time to death from any cause	0.77 (0.56, 1.06)	0.84 (0.76, 0.93)	0.91 (0.65, 1.28)	1.41

Source: Table 2.6-3, p.97 of the submission.
Abbreviations: ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CI, confidence interval; CV, cardiovascular; ESS, effective sample size; HF, heart failure; HR, hazard ratio; SOC, standard care.

6.29 There were no statistically significant differences between dapagliflozin and sacubitril/valsartan for the composite outcome of time to cardiovascular death or hospitalisation for heart failure, time to hospitalisation for heart failure, time to cardiovascular death, or time to death from any cause based on the MAIC using DAPA-HF subgroups.

6.30 For the composite of time to cardiovascular death or hospitalisation for heart failure, and the time to cardiovascular death, the upper 95% confidence interval exceeded or equalled the non-inferiority margin proposed in the submission. The upper 95% confidence interval for time to death from any cause was less than the non-inferiority margin proposed in the submission. No non-inferiority margin was proposed for time to hospitalisation for heart failure.

6.31 The evaluation considered the results of the MAIC to be uncertain due to residual differences between the trials, potential bias introduced by the use of post hoc

subgroups, and the large loss of sample size after matching. However, the ESC considered the results across the ITCs for the total population and the subgroup from DAPA-HF, as well as the MAIC, generated reasonably consistent results.

Comparative harms

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

Table 8: Summary of key adverse events in the DAPA-HF trial (on treatment period)

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

Source: Table 2.5-7, p.86 of the submission.
Abbreviations: AE, adverse event; SOC, standard care.
[1] Events adjudicated as definite or probable diabetic ketoacidosis.
[2] AE with the following criteria confirmed by the investigator: i) Symptoms of severe impairment in consciousness or behaviour ii) need of external assistance iii) intervention to treat hypoglycaemia iv) prompt recovery of acute symptoms following the intervention.
[3] Based on pre-defined list of preferred terms.
[4] Surgical or spontaneous/non-surgical amputation, excluding amputation due to trauma.

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

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

6.35 Comparison of safety outcomes for the DAPA-HF and PARADIGM-HF trials was limited due to differences in safety outcome reporting between the trials. While both trials reported serious adverse events, adverse events of any severity were only available for the DAPA-HF trial if they were included as part of the definition of an adverse event of special interest.

6.36 Table 9 presents a naïve comparison of treatment emergent adverse events (where available) and serious adverse events for the DAPA-HF and PARADIGM-HF trials.

Table 9: Naïve comparison of adverse events for the DAPA-HF and PARADIGM-HF trials

AE category	DAPA-HF		PARADIGM-HF	
	Dapagliflozin + SOC (N=2368)	Placebo + SOC (N=2368)	Sacubitril/ valsartan + SOC (N=4203)	Enalapril + SOC (N=4229)
Median duration of follow-up, months (range)	18.3 (0.0-27.3)	18.2 (0.2-27.8)	27.2 (NR)	27.0 (NR)
Adverse events of any grade				
Hypotension, n (%)	92 (3.9)	80 (3.4)	740 (17.6)	506 (12.0)
Cardiac failure, n (%)	291 (12.3)	405 (17.1)	730 (17.4)	832 (19.7)
Hyperkalaemia, n (%)	30 (1.3)	38 (1.6)	488 (11.6)	592 (14.0)
Renal impairment, n (%)	66 (2.8)	63 (2.7)	426 (10.1)	487 (11.5)
Dizziness, n (%)	44 (1.9)	28 (1.2)	251 (6.0)	236 (5.6)
Atrial fibrillation, n (%)	80 (3.4)	82 (3.5)	251 (6.0)	236 (5.6)
Pneumonia, n (%)	93 (3.9)	98 (4.1)	227 (5.4)	237 (5.6)
Peripheral oedema, n (%)	13 (0.5)	27 (1.1)	215 (5.1)	213 (5.0)
Dyspnoea, n (%)	21 (0.9)	37 (1.6)	213 (5.1)	306 (7.2)
Bronchitis, n (%)	30 (1.3)	26 (1.1)	183 (4.4)	224 (5.3)
Serious adverse events ≥2%				
Cardiac failure, n (%)	238 (10.1)	325 (13.7)	588 (14.0)	649 (15.3)
Pneumonia, n (%)	70 (3.0)	73 (3.1)	155 (3.7)	181 (4.3)
Cardiac failure (chronic), n (%)	24 (1.0)	26 (1.1)	112 (2.7)	135 (3.2)
Cardiac failure (congestive), n (%)	57 (2.4)	65 (2.7)	112 (2.7)	140 (3.3)
Atrial fibrillation, n (%)	23 (1.0)	37 (1.6)	108 (2.6)	113 (2.7)
Cardiac death, n (%)	17 (0.7)	27 (1.1)	85 (2.0)	114 (2.7)
Cardiac failure (acute), n (%)	36 (1.5)	51 (2.2)	67 (1.6)	93 (2.2)
Ventricular tachycardia, n (%)	32 (1.4)	53 (2.2)	66 (1.6)	85 (2.0)

Source: Table 5, p.32; Table 6, p.33 of Attachment 2.5 of the submission.
Abbreviations: AE, adverse event; NR, not reported.

6.37 The results of the safety comparisons should be interpreted with caution due to the inclusion of the run-in phase in the PARADIGM-HF trial, and large differences in follow-up durations between the trials (median of 18 months for DAPA-HF versus median of 27 months for PARADIGM-HF). There may also have been differences in the

adjudication of the adverse events due to the definition of the events in the DAPA-HF trial as components of the adverse events of special interest.

6.38 The submission also presented the results of indirect and matching adjusted indirect comparisons of serious adverse events occurring in ≥2% of patients in the DAPA-HF and PARADIGM-HF trials. These comparisons of serious adverse events were not considered informative due to the predominance of heart failure-related events among the serious adverse events.

Benefits/harms

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

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

6.40 A comparison of benefits and harms for dapagliflozin plus standard care versus sacubitril/valsartan plus standard care has not been presented, given the submission's claim of non-inferior effectiveness and safety.

Clinical claim

6.41 The submission described dapagliflozin added to standard care (comprising an ACE inhibitor or ARB, a beta-blocker, and, if appropriate, an MRA), as non-inferior, in terms of effectiveness and safety, compared to sacubitril/valsartan added to standard care (comprising a beta-blocker; and, if appropriate, an MRA) when used in the management of patients with heart failure with reduced ejection fraction. The definition of standard care in the DAPA-HF and PARADIGM-HF trials was broader than defined in the submission's clinical claim. In addition to the minimum treatments specified in the trial eligibility criteria (ACE inhibitor, ARB or sacubitril/valsartan; a beta-blocker; and, if appropriate, an MRA), patients in the trials also continued other background heart failure treatments, such as digoxin, ivabradine, vasodilators, and diuretics.

6.42 This claim was generally adequately supported with the following concerns noted during the evaluation and by ESC:

- There were some differences between the DAPA-HF and PARADIGM-HF trials in trial design (run-in periods), common reference arms (placebo plus standard care versus fixed-dose enalapril plus standard care), patient characteristics (mean age, mean LVEF, background therapies, heart failure severity, proportion of patients with diabetes), follow-up durations (18 months versus 27 months), and trial locations (20 countries versus 47 countries). The ESC considered these differences may have affected the reliability of the indirect comparisons presented in the

submission but were unlikely to have had a major impact. Indirect comparisons based on post hoc DAPA-HF subgroups may have introduced bias into the comparisons.

- The submission addressed some of the differences in eligibility criteria and patient characteristics by conducting a MAIC, based on selected subgroups of patients from the DAPA-HF trial. However, the evaluation considered the results of the MAIC to be uncertain due to residual differences between the trials, potential bias introduced by the use of post hoc subgroups, and the small sample size after matching. The ESC considered the reduced sample was not a major issue if the common reference arms anchoring the MAIC were considered acceptable.
- The ESC considered the applicability of the nominated non-inferiority margin for the primary outcome of cardiovascular death and hospitalisation for heart failure was reasonable, based on a prior heart failure study. However, the applicability of the nominated non-inferiority margins for time to cardiovascular death and time to death from any cause was not justified or reasonable, as they were not derived from heart failure trials, and were not derived for the same outcomes.
- Comparison of safety outcomes was necessarily limited due to differences in outcome reporting between the trials.

6.43 The submission also described dapagliflozin added to standard care (comprising an ACE inhibitor, ARB, or sacubitril/valsartan; a beta-blocker; and, if appropriate, an MRA), as superior in terms of effectiveness to standard care alone (comprising an ACE inhibitor, ARB or sacubitril/valsartan; a beta-blocker; and, if appropriate, an MRA) when used in the management of patients with heart failure with reduced ejection fraction.

6.44 Based on this broader definition of standard care (comprising an ACE inhibitor, ARB or sacubitril/valsartan; a beta-blocker; and, if appropriate, an MRA along with other heart failure treatments), the claim of superior comparative effectiveness was considered to be adequately supported during the evaluation:

- Treatment with dapagliflozin (plus standard care) was associated with statistically significant reductions in the primary composite outcome of time to cardiovascular death, hospitalisation due to heart failure, or an urgent heart failure visit, and the secondary composite outcome of time to cardiovascular death or hospitalisation due to heart failure, compared to placebo (plus standard care). The treatment effect appeared to be consistent across diabetic and non-diabetic subgroups.
- The ESC noted the TGA Evaluators' concerns with regard to a lower outcome benefit seen with dapagliflozin in the DAPA-HF trial for NYHA Class III/IV patients compared to NYHA Class II patients, with the NYHA Class III/IV subgroup not achieving statistical significance. This could possibly represent a greater benefit in patients earlier in the disease course. While this represents a subgroup analysis, the ESC noted that 32% of patients in DAPA-HF were Class III/IV. The pre-PBAC response stated that although the results suggest less treatment benefit in the

NYHA subgroups Class III-IV compared with Class II, findings with respect to other advanced disease subgroups did not show a reduced treatment effect by HF severity. For example, it claimed that dapagliflozin reduced the risk of the primary composite outcome regardless of baseline HF severity as measured by NT-proBNP, LVEF, prior hospitalisation for HF, and KCCQ-TSS.

6.45 The submission did not include an explicit safety claim for dapagliflozin (plus standard care) versus placebo (plus standard care). The pre-PBAC response claimed that dapagliflozin plus standard of care is non-inferior to standard of care alone in terms of safety outcomes. Comparison of safety outcomes was limited to serious adverse events and adverse events of special interest. While a comparison of serious adverse events numerically favoured dapagliflozin, most of the difference appeared to be driven by heart failure-related events.

6.46 The submission did not include a specific claim regarding comparative effectiveness of concomitant or sequential treatment of dapagliflozin and sacubitril/valsartan compared to sacubitril/valsartan, although the proposed PBS restriction would allow this. Around 11% of patients were receiving sacubitril/valsartan as background therapy in DAPA-HF.

6.47 The PBAC considered that it was reasonable to claim superior comparative effectiveness of dapagliflozin added to standard care (comprising an ACE inhibitor, ARB, or sacubitril/valsartan; a beta-blocker; and, if appropriate, an MRA), compared to standard care alone (comprising an ACE inhibitor, ARB or sacubitril/valsartan; a beta-blocker; and, if appropriate, an MRA). The safety claim of non-inferiority was probably reasonable, although predominantly due to fewer heart failure events in the dapagliflozin arm, due to its superior efficacy over standard care.

6.48 However, the PBAC also considered that this therapeutic conclusion was not appropriately considered in the economic analysis (see section 7 PBAC outcome).

Economic analysis

6.49 The submission presented a cost-minimisation analysis comparing dapagliflozin (plus standard care) with sacubitril/valsartan (plus standard care).

6.50 The submission claimed that a cost-effectiveness analysis versus standard care was not required given that sacubitril/valsartan has previously demonstrated cost-effectiveness versus standard care, and based on the claim of non-inferiority of dapagliflozin versus sacubitril/valsartan made in the submission. However, the PBAC

agreed with the evaluation and the ESC that this was not reasonable due to the following reasons:

- Dapagliflozin and sacubitril/valsartan have different mechanisms of action and are likely to be used in different populations.
- The cost-effectiveness of dapagliflozin (added to standard care) versus standard care alone (which may include treatment with sacubitril/valsartan) has not been established.
- The cost-effectiveness of concomitant use of dapagliflozin and sacubitril/valsartan has not been established.

6.51 The ESC advised the cost-minimisation to sacubitril/valsartan was not well supported, given dapagliflozin is likely to be used in a broader population than sacubitril/valsartan. Given that dapagliflozin has a different mechanism of action compared to sacubitril/valsartan, patients will potentially switch from, add-on, or displace sacubitril/valsartan, or grow the current heart failure market. This complexity makes undertaking a cost-minimisation analysis comparing dapagliflozin (plus standard care) with sacubitril/valsartan (plus standard care) difficult for establishing a cost-effective price for dapagliflozin in this clinical setting.

6.52 The ESC advised that a cost-utility analysis comparing dapagliflozin plus standard care (comprising of a beta blocker, plus ACE-I/ ARB) to standard care (beta blocker, plus ACE-I/ ARB) would be necessary to support the expected majority use of dapagliflozin. The cost-effectiveness of dapagliflozin (added to standard care which includes sacubitril/valsartan) versus standard care alone (which includes treatment with sacubitril/valsartan), would also be informative; as would the cost-effectiveness of concomitant use of dapagliflozin and sacubitril/valsartan.

6.53 The pre-PBAC response argued that cost-effectiveness of dapagliflozin in the population of patients who may 'add-on' dapagliflozin to sacubitril/valsartan or for whom dapagliflozin will 'displace' sacubitril/valsartan, may be informed by two recently published cost-effectiveness analyses (Savira et al, 2020 and McEwan et al, 2020). In particular, it noted that the CEA based on the Australian healthcare setting using up-to-date Australian inputs, and based on the current price of dapagliflozin in T2DM, resulted in dapagliflozin having a discounted incremental cost-effectiveness ratio of $12,482 per quality-adjusted life year gained (Savira et al, 2020). The pre-PBAC response reaffirmed the PSCR view that co-administration is unlikely to occur in greater than 20% of the population in the Australian setting (a figure based on the EMPEROR-Reduced trial (Packer et al, 2020) and clinical advice).

6.54 The PBAC considered a fully evaluated cost-effectiveness analysis was required.

Drug cost/patient/year

6.55 The estimated drug cost per patient per year for dapagliflozin was $[redacted] (based on the proposed published DPMQ of $[redacted] for 28 tablets; 13.04 scripts per year). The

estimated drug cost per patient per year for dapagliflozin incorporating the submission's assumed compliance rate of 95% was $[redacted]. Patients treated with dapagliflozin would also require treatment with an ACE inhibitor, ARB or sacubitril/valsartan.

6.56 The estimated drug cost per patient per year for sacubitril/valsartan was $2,646 (based on the published DPMQ of $202.89 for 56 tablets; 13.04 scripts per year). The estimated drug cost per patient per year for sacubitril/valsartan incorporating the submission's assumed compliance rate of 75% was $1,984.

Estimated PBS usage & financial implications

6.57 The submission was considered by DUSC. The submission used a mixed epidemiological/market share approach to estimate the utilisation and financial impacts associated with the PBS listing of dapagliflozin for the treatment of chronic heart failure with reduced ejection fraction.

Table 10: Key inputs for the financial estimates

Parameter	Value applied and source	Comment
Incident HF patients	Prevalence of 1.5% based on a systematic review of studies reporting on the prevalence of heart failure in Australia between 1990 and 2015 (Sahle et al., 2016). The reported prevalence ranged from 1.0-2.0%.	The National Heart Foundation guidelines suggest that based on international prevalence rates, there were an estimated 480,000 people aged ≥18 years with heart failure in 2014, representing 2.1% of the Australian adult population.
Proportion of patients with HFrEF	64% based on medical records of patients discharged with a primary diagnosis of HF from hospitals in Minneapolis-St Paul (Minnesota, US) in 1995 and 2000 (Adabag et al., 2012).	HFrEF was defined as a LVEF <45%, which differed from the proposed restriction (≤40%). The proportions were derived from hospitalised heart failure patients which may not be representative of the general heart failure population. The applicability of the US-based data was unclear.
Proportion of patients with NYHA class II-IV	95% based on the proportion of patients with class II-IV heart failure used in the July 2016 sacubitril/valsartan resubmission.	The evaluation considered that this assumption appeared reasonable.
Proportion of patients treated with standard care	95% based on sponsor assumption. The submission argued that the proportion of patients not receiving standard care would be less than 100% based on inability to tolerate standard care treatments, or choice not to be treated with standard.	The evaluation considered that this proportion was uncertain, and may overestimate the proportion of patients receiving optimised standard care.
Proportion of patients receiving a SGLT2 for diabetes	11.6% derived from a 10% Medicare analysis of patients co-administering sacubitril/valsartan and an SGLT-2 inhibitor.	There was a lack of documentation regarding the methods used in the analysis, including the definitions used to identify co-administration of therapies.
Estimated annual rate of growth of sacubitril/ valsartan market (from previous year to nominated year)	A rolling annual growth rate was derived from available PBS/RPBS dispensing data for sacubitril/valsartan (January 2017 to April 2020). An exponential curve was fitted to the data points. The growth rate was assumed to decline until the rate of growth of the Australian population (1.5%) was reached, where it was assumed to stabilise.	Sacubitril/valsartan was PBS listed in June 2017. Therefore, there is limited available data to inform future growth. The evaluation considered that the assumption of an exponential curve with a 1.5% floor may underestimate the future growth of sacubitril/valsartan.

Parameter	Value applied and source	Comment
Dapagliflozin uptake (additional eligible patients)	Yr 1: 5%; Yr 2: 18%; Yr 3: 22%; Yr 4: 28%; Yr 5: 35%; Yr 6: 42%. Based on sponsor assumption.	Uptake rates were considered uncertain given that the place of dapagliflozin in therapy is currently unclear.
Dapagliflozin uptake (sacubitril/ valsartan patients)	Yr 1: 4%; Yr 2: 7%; Yr 3: 14%; Yr 4: 16%; Yr 5: 18%; Yr 6: 22%. Based on sponsor assumption.	Uptake rates were considered uncertain given that the place of dapagliflozin in therapy is currently unclear. The submission did not account for potential co-administration of sacubitril/valsartan and dapagliflozin.
Sacubitril/ valsartan compliance	75% based on the sacubitril/valsartan PBAC public summary document (July 2016).	Differences in the assumed compliance between dapagliflozin and sacubitril/valsartan may be overestimated.
Dapagliflozin compliance	95% based on sponsor assumption. The submission predicted better compliance with dapagliflozin compared to sacubitril/valsartan.	Differences in the assumed compliance between dapagliflozin and sacubitril/valsartan may be overestimated.
Dapagliflozin price	$[redacted] (proposed dapagliflozin AEMP)	The submission noted that sacubitril/valsartan is subject to a special pricing arrangement and that the dapagliflozin price would be derived using the proposed cost-minimisation analysis based on the effective price of sacubitril/valsartan minus the cost of valsartan.
Sacubitril/valsartan price	$173.49 (published sacubitril/valsartan AEMP)	The submission noted that sacubitril/valsartan is subject to a special pricing arrangement.

Source: Figure 4.1-1, p.125 of the submission; 'Key Inputs' worksheet of the Section 4 financial Excel workbook.
Abbreviations: ABS, Australian Bureau of Statistics; ACE, angiotensin-converting enzyme; AEMP, Approved ex-manufacturer price; ARB, angiotensin II receptor blocker; GP, General Practitioner; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SGLT2, sodium-glucose co-transporter-2; Yr, Year.

6.58 Table 11 presents the estimated net cost to the PBS/RPBS of listing dapagliflozin for the treatment of patients with chronic heart failure with reduced ejection fraction.

Table 11: Financial impact of listing dapagliflozin for chronic heart failure with reduced ejection fraction

	Year 1 (2021)	Year 2 (2022)	Year 3 (2023)	Year 4 (2024)	Year 5 (2025)	Year 6 (2026)
Dapagliflozin scripts						
Total treated patients	[redacted][1]	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][4]	[redacted][5]
Total dapagliflozin scripts	[redacted][6]	[redacted][7]	[redacted][8]	[redacted][9]	[redacted][10]	[redacted][11]
PBS/RPBS cost ($[redacted] per script)	$[redacted][12]	$[redacted][13]	$[redacted][14]	$[redacted][15]	$[redacted][16]	$[redacted][17]
Patient co-payment ($13.25 per script)	$[redacted][1][8]	$[redacted][1][8]	$[redacted][18]	$[redacted][18]	$[redacted][18]	$[redacted][18]
Net PBS/RPBS cost of dapagliflozin	$[redacted][12]	$[redacted][13]	$[redacted][19]	$[redacted][15]	$[redacted][16]	$[redacted][17]
Displaced SAC/VAL scripts						
Displaced SAC/VAL scripts	[redacted][18]	[redacted][4]	[redacted][6]	[redacted][19]	[redacted][19]	[redacted][19]
PBS/RPBS cost ($202.89 per script)	$[redacted][20]	$[redacted][2][0]	$[redacted][12]	$[redacted][21]	$[redacted][21]	$[redacted][21]
Patient co-payment ($13.25 per script)	$[redacted][20]	$[redacted][20]	$[redacted][20]	$[redacted][20]	$[redacted][2][0]	$[redacted][20]
Total cost displaced SAC/VAL	$[redacted][20]	$[redacted][20]	$[redacted][12]	$[redacted][12]	$[redacted][21]	$[redacted][21]
Net cost to the PBS/RPBS						
Cost of listing dapagliflozin	$[redacted][12]	$[redacted][1][3]	$[redacted][22]	$[redacted][15]	$[redacted][16]	$[redacted][17]
Net PBS/RPBS cost of displaced sacubitril/valsartan	$[redacted][20]	$[redacted][2][0]	$[redacted][1][2]	$[redacted][12]	$[redacted][21]	$[redacted][21]
Net cost to PBS/RPBS	**$**[redacted][12]	**$**[redacted][23]	**$**[redacted][13]	**$**[redacted][22]	**$**[redacted][14]	**$**[redacted][24]
Net saving to MBS	$[redacted][20]	$[redacted][20]	$[redacted][20]	$[redacted][20]	$[redacted][20]	$[redacted][20]
Net cost to Government	$[redacted][12]	$[redacted][23]	$[redacted][13]	$[redacted][22]	$[redacted][14]	$[redacted][24]

Source: Table 4.2.4, p.130; Table 4.2.5, p.130; Table 4.2.6, p.132; Table 4.3.1, p.132; Table 4.3.2, p.133; Table 4.5.3, p.136 of the submission.
Abbreviations: SAC/VAL, sacubitril/valsartan.

The redacted values correspond to the following ranges:
[1]5,000 to <10,000
[2]20,000 to <30,000
[3]30,000 to <40,000
[4]40,000 to <50,000
[5]50,000 to <60,000
[6]80,000 to < 90,000
[7]200,000 to <300,000
[8]300,000 to <400,000
[9]400,000 to <500,000
[10]500,000 to <600,000
[11]600,000 to <700,000
[12]$10 million to <$20 million
[13]$40 million to <$50 million
[14]$60 million to <$70 million
[15]$70 million to <$80 million
[16] $90 million to <$100 million
[17]$100 million to <$200 million
[18]10,000 to <20,000
[19]100,000 to <200,000
[20]$0 to <$10 million
[21]$20 million to <$30 million
[22]$50 million to <$60 million
[23]$30 million to <$40 million[24]$80 million to <$90 million

6.59 At year 6, the estimated number of patients was 50,000 to <60,000 and the net cost to the PBS/RPBS would be $80-90 million. There as an estimated net cost to the PBS/RPBS of $200 to <$300 million over the first six years of listing. The PBAC noted these costs were based on the published price of the comparator. The net cost to the PBS would reduce once the effective price of the comparator was applied.

6.60 DUSC considered that the estimates presented in the submission were underestimated. The main issues were:

- The risk of leakage is likely to be high as dapagliflozin is already well-known to prescribers and evidence shows positive outcomes for cardiovascular disease, heart failure with reduced/preserved ejection fraction and potentially chronic kidney disease. There may also be an increase in patients utilising the diabetes restriction due to these positive outcomes for other diseases.
- The submission provided no estimates with regards to patients who may use both dapagliflozin and sacubitril/valsartan and acknowledged that even 20% of patients using both could still be a substantial cost to the PBS.
- The incidence of heart failure was underestimated. Altering the prevalence rate from 1.5% to 2.199% (as reported by the SHAPE study) changed the prevalence of heart failure in Australia to 450,000 people instead of the submissions proposed 306,449. Accepting this alteration in the financial workbook changed the total six year PBS cost from $200 to 300 million to $500 to 600 million.
- The assumption of the proportion of heart failure patients who have heart failure with reduced ejection fraction (HFrEF) as 64% may be overestimated. Data from an analysis on the SHAPE study suggests that 62% of heart failure patients may be considered HFrEF and data from the SNAPSHOT-HF study suggests 58% of acute heart failure admissions were HFrEF. Altering this proportion of patients to 60% resulted in a reduction in the six year net PBS costs from $200-300 million to $200-300 million.

- Uptake is likely to be higher as dapagliflozin is already well-known to prescribers with a favourable safety profile relative to sacubitril/valsartan. Uptake for patients switching from sacubitril/valsartan was unjustified and likely to be overestimated as patients would be switching from stable therapy. It would be more likely that dapagliflozin would be added on to therapy in these patients if needed.
- Dapagliflozin may have greater compliance due to once daily dosing compared to twice daily dosing of sacubitril/valsartan. However an adherence of 95% compared to 75% is likely an overestimate. Moreover, the method used to derive the number of dapagliflozin scripts due to substitution for sacubitril/valsartan resulted in an assumption of equal compliance for sacubitril/valsartan and

dapagliflozin, which was not consistent with the compliance assumptions used for dapagliflozin treated patients in the additional eligible population. The DUSC considered that compliance assumptions should be consistent across calculations.

6.61 The evaluation had additionally noted that:

- There was a risk of use outside of the proposed restriction, among patients with HFpEF, NYHA Class I heart failure, patients not receiving optimal therapy with an ACE inhibitor and cardio-selective beta blocker, and patients with heart failure with moderately reduced ejection fraction (LVEF of 40-49%).
- The estimates did not account for an additional cost of ACE inhibitor/ARB therapy among patients who switch from sacubitril/valsartan to dapagliflozin.
- The estimates did not account for substitution of dapagliflozin for other heart failure therapies such as MRAs, digoxin, ivabradine or hydralazine plus isosorbide dinitrate.

Quality Use of Medicines

6.62 No quality use of medicines issues were identified in the submission, and no activities to support the quality use of medicines were proposed.

6.63 The following quality use of medicines issues were noted during the evaluation and by DUSC:

- Patients may initiate dapagliflozin despite not being on optimised treatment with an ACE inhibitor or ARB, a beta blocker, and (if appropriate) an MRA.
- Patients switching from sacubitril/valsartan to dapagliflozin may neglect to recommence treatment with an ACE inhibitor or ARB.
- The dapagliflozin product information states that dapagliflozin should not be used to improve glycaemic control in patients with an eGFR persistently less than 45 mL/min/1.73 m2, as the glycaemic efficacy of dapagliflozin is dependent on renal function. While the DAPA-HF Trial included patients with an eGFR of at least 30 mL/min/1.73m2, it is unclear whether an eGFR of >30 and < 45 mL/min/1.73 m2 would affect the efficacy of dapagliflozin in the management of heart failure.
- Patients switching from sacubitril/valsartan to dapagliflozin are likely to require additional monitoring due to the potential for exacerbation of heart failure during cessation of sacubitril/valsartan, restabilisation on an ACE inhibitor or ARB, and initiation of dapagliflozin.
- There is a potential risk of volume depletion associated with the use of multiple diuretic agents, including dapagliflozin, loop diuretics and MRAs.
- Urinary tract infections are an important identified risk of dapagliflozin. Treatment of urinary tract infections with trimethoprim may increase the risk of

hyperkalaemia due to interaction with other heart failure medications (ACE inhibitor/ARB, MRA).

- There may be potential for inadvertent co-prescribing of dapagliflozin with other SGLT2 inhibitors used for the treatment of diabetes.
- There is a definite risk of diabetic ketoacidosis when SGLT2 inhibitors are taken by patients undergoing surgical procedures causing unexpected delays in surgeries. Patients should be informed upon commencement of these medications.

Financial Management – Risk Sharing Arrangements

6.64 No risk-sharing arrangement (RSA) was proposed in the submission. However, the PSCR indicated that the sponsor was willing to accept the current RSA in place for sacubitril/valsartan as an RSA to cover both dapagliflozin and sacubitril/valsartan. The ESC noted that, should dapagliflozin be approved under this RSA, any other ARNIs or SGLT2-inhibitors subsequently approved for this indication should also be encompassed in the same RSA.

6.65 In the July 2016 consideration of sacubitril/valsartan, the PBAC noted that the submission's model structure was unchanged from the March 2016 major submission, and recalled that it was previously concerned that the model did not accurately reflect the disease progression of patients with heart failure and the baseline heart failure mortality was not reflective of that for the likely PBS population. The PBAC considered that it would be appropriate to reduce the price of sacubitril/valsartan to the price of enalapril beyond an expenditure cap. Specifically, the PBAC recalled the previous sensitivity analyses and sought to be reassured that, at the revised price, cost effectiveness was likely to remain acceptable using model inputs more likely to reflect the PBS population (Paragraph 7.1, sacubitril/valsartan, Public Summary Document, July 2016).

6.66 Sacubitril/valsartan was subsequently recommended in August 2016 based on a reduced price, and a proposed RSA including a two-tier financial cap (Addendum, sacubitril/valsartan, Public Summary Document, July 2016 PBAC meeting).

6.67 The PBAC did not consider it appropriate for dapagliflozin to share the caps in the sacubitril/valsartan RSA (see section 7).

7 PBAC Outcome

7.1 The PBAC did not recommend dapagliflozin for the treatment of patients with chronic heart failure with reduced ejection fraction. The PBAC considered that although dapagliflozin was effective for this indication, its clinical place was unclear and likely to evolve. The selection of sacubitril/valsartan as the main comparator was inappropriate, and hence the economic analysis presented in the submission did not allow for an assessment of cost effectiveness. The PBAC considered the cost-effectiveness of dapagliflozin added to standard care (comprising a beta-blocker plus

an ACE inhibitor or ARB) versus standard care alone (comprising a beta-blocker plus an ACE inhibitor or ARB) would need to be established in a future resubmission. An additional cost-effectiveness analysis is also required for concomitant use of dapagliflozin and sacubitril/valsartan (plus a beta-blocker) compared to sacubitril/valsartan (plus a beta-blocker), which would be allowed under the proposed PBS listing.

7.2 The PBAC noted that the submission positioned dapagliflozin as an alternative or add-on option to sacubitril/valsartan when intensification of treatment is required following stabilisation on therapy with an ACE inhibitor/ARB, a beta-blocker and a MRA. However, the PBAC considered that the clinical place for dapagliflozin is not yet established and will evolve over time, noting that:

- The National Heart Foundation guidelines (2018) do not contain specific recommendations for the use of SGLT2 inhibitors in the treatment of established heart failure.
- There was a major submission to the November 2020 PBAC meeting, which sought to include a broader population of patients in the current sacubitril/valsartan PBS listing.
- The substantial diuretic effect of dapagliflozin may influence the position of MRAs and other diuretics.
- Sacubitril/valsartan and dapagliflozin have different optimal patient profiles and dapagliflozin was more likely to be used in patients with diabetes, normotension/relative or fluid overload, whereas sacubitril/valsartan may be preferred for use in patients with hypertension.

7.3 The PBAC agreed with the ESC that given that dapagliflozin has a different mechanism of action compared to sacubitril/valsartan, patients will potentially switch from, add-on, or displace sacubitril/valsartan, or grow the current heart failure market.

7.4 The PBAC noted that the submission nominated sacubitril/valsartan as a major comparator, and standard of care (which may or may not include sacubitril/valsartan) as a minor comparator. The PBAC also noted that the majority of patients in the DAPA-HF trial were not using an ARNI as part of standard care (approximately 89%). The PBAC agreed with the ESC that this would likely reflect Australian clinical practice, and thus considered that the appropriate comparator for the majority of dapagliflozin use would be 'standard of care' consisting of an ACE inhibitor (or ARB) and a beta blocker. MRAs and other background heart failure therapies could be considered as part of this standard of care, but noting the variability of current care, the PBAC viewed that they would complicate a cost-effectiveness comparison and could potentially be excluded if their financial impact were minor.

7.5 Complementary to this, the PBAC considered that 'standard of care plus sacubitril/valsartan' (i.e. a beta blocker plus sacubitril/valsartan) would be an appropriate comparator for a minor proportion of the proposed population. The PBAC

considered that this portion could be *reasonably* estimated as somewhere between 11% (the proportion in the DAPA-HF trial using both dapagliflozin and sacubitril/valsartan at baseline) and 20% (the proportion of concomitant use estimated in the PSCR and pre-PBAC response, based on the EMPEROR-Reduced trial and clinical opinion).

7.6 Based on the key trial, DAPA-HF, treatment with dapagliflozin (plus standard care) was associated with statistically significant reductions in the primary composite outcome of time to cardiovascular death, hospitalisation due to heart failure, or an urgent heart failure visit, and the secondary composite outcome of time to cardiovascular death or hospitalisation due to heart failure, compared to placebo (plus standard care). The PBAC noted the treatment effect appeared to be consistent across diabetic and non-diabetic subgroups.

7.7 The PBAC considered it was reasonable to claim that based on the DAPA-HF trial, dapagliflozin added to standard care (comprising an ACE inhibitor, ARB or sacubitril/valsartan; a beta-blocker; and, if appropriate, an MRA along with other heart failure treatments) was superior compared with standard care alone. Whilst noting the TGA Evaluators' concerns with regard to a lower outcome benefit seen with dapagliflozin in the DAPA-HF trial for NYHA Class III/IV patients compared to NYHA Class II patients, the PBAC also noted the pre-PBAC response, which highlighted that findings with respect to other advanced disease subgroups did not show a reduced treatment effect by HF severity.

7.8 The PBAC considered the claim of non-inferior safety was also reasonable.

7.9 The PBAC did not consider the ITC comparisons to sacubitril/valsartan were relevant for decision-making.

7.10 The submission presented a cost-minimisation analysis comparing dapagliflozin (plus standard care) with sacubitril/valsartan (plus standard care). The PBAC considered that the economic analysis was not informative because:

- It was not based on the appropriate main comparator (see paragraph 7.4).
- The cost-effectiveness of dapagliflozin (added to standard care) versus standard care alone has not been established.
- The cost-effectiveness of concomitant use of dapagliflozin and sacubitril/valsartan has not been established.

7.11 The PBAC agreed with the ESC that a cost-utility analysis comparing dapagliflozin plus standard care (comprising of a beta blocker, plus ACE-inhibitor/ARB) to standard care (beta blocker, plus ACE-inhibitor/ARB) would be necessary to support the expected majority use of dapagliflozin (approximately 80-89%, based on the DAPA-HF and EMPEROR-Reduced trials). Complimentarily, for 11-20% of the expected PBS use, a cost-effectiveness analysis comparing dapagliflozin added to standard care (comprising of a beta-blocker, plus sacubitril/valsartan) versus standard care alone

(comprising of a beta-blocker, plus sacubitril/valsartan), would also be necessary to account for the concomitant use of dapagliflozin and sacubitril/valsartan.

7.12 The PBAC noted the DUSC's advice that the financial estimates were likely underestimated, and agreed that there were a number of issues including a high risk of leakage in earlier stages of disease, underestimated uptake rates, and a lack of accounting for concomitant use of dapagliflozin and sacubitril/valsartan. Furthermore, the PBAC expressed concern around the QUM issues expressed in paragraph 6.62, noting that these were not identified or addressed in the submission.

7.13 The PBAC also rejected the submission's proposal to share the caps of the current risk-sharing arrangement for sacubitril/valsartan. A separate and distinct RSA for dapagliflozin would be required.

7.14 In view of the above, the PBAC considered that any resubmission would need to be a major submission, presenting a modelled economic evaluation as outlined in paragraph 7.11, and addressing DUSC's concerns, including the QUM issues identified.

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

Outcome:
Rejected

8 Context for Decision

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

9 Sponsor's Comment

The sponsor had no comment.