

5.20 VERICIGUAT, Tablet 2.5 mg, Tablet 5 mg, Tablet 10 mg, Verquvo[®], Bayer Australia Limited.

1 Purpose of submission

- 1.1 The Category 2 submission requested an Authority Required (Streamlined) listing of vericiguat for the treatment of patients with symptomatic chronic heart failure (NYHA class II, III and IV) with reduced ejection fraction (LVEF <45%) who are stabilised after a recent decompensation event requiring hospitalisation and/or intravenous diuretic therapy and are on concomitant standard of care (SoC) therapies.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis for vericiguat plus SoC versus placebo plus SoC.

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

Component	Description
Population	Adult patients with symptomatic (NYHA class II, III or IV) chronic heart failure with reduced ejection fraction (HFrEF, LVEF <45%) who are stabilised after a recent decompensation event requiring hospitalisation and/or intravenous diuretic therapy
Intervention	Vericiguat 2.5 mg up-titrated to 10 mg once daily, with concomitant use of standard of care therapies
Comparator	Placebo plus standard of care (SoC). SoC therapies include ACEi/ARB or ARNi, beta-blocker, MRA, diuretics
Outcomes	Primary composite outcome of cardiovascular death and hospitalisation for heart failure, and secondary or exploratory outcomes of time to cardiovascular death, time to first and subsequent heart failure hospitalisation, quality of life outcomes, and safety
Clinical claim	Vericiguat plus standard of care is superior in terms of efficacy and comparable in terms of safety compared to placebo plus standard of care

Source: Table 1-1, p31 of the submission

2 Background

Registration status

- 2.1 Vericiguat was submitted under the TGA/PBAC parallel process, via the Access Consortium New Active Substance work-sharing initiative, divided across three regulatory agencies (TGA Australia, Swissmedic Switzerland, Singapore Health Sciences Authority Singapore).
- 2.2 Vericiguat was listed on the Australian Register of Therapeutic Goods (15 November 2021) for the following indication:
- In addition to standard of care therapy for the treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction less than 45% who are stabilised

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after a recent heart failure decompensation event requiring admission and/or IV diuretic therapy.

2.3 Vericiguat has not previously been considered by the PBAC.

3 Requested listing

3.1 The restriction proposed in the submission is outlined below with the amendments advised by the PBAC in italics (additions) and strikethrough (deletions).

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
VERICIGUAT				
Film-coated tablets				
2.5 mg	28	5		Verquvo®,
5 mg	28	5	\$	Bayer Australia Limited
10 mg	28	5		

Restriction Summary / Treatment of Concept:
Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required (Streamlined) [new code] <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)
Severity: Chronic
Condition: Chronic heart failure
Indication: Chronic heart failure
Treatment Phase: Initial treatment
Treatment criteria
<i>Must be initiated under the supervision of a specialist cardiologist</i>
Clinical criteria:
Patient must be symptomatic with NYHA classes II, III or IV
AND
Clinical criteria:
Patient must have a documented left ventricular ejection fraction (LVEF) of less than 45%
AND
Clinical criteria:
Patient <i>The condition must be stabilised after recent following a decompensation event that required requiring either (i) hospitalisation in the past 6 months, (ii) and/or IV intravenous diuretic therapy in the past three months</i>
AND
Clinical criteria:
<i>Patient must not have clinical signs of fluid overload</i>
AND
Clinical criteria:
<i>Patient must not have received intravenous treatment in the previous 24 hours</i>
AND
Clinical criteria:
<i>Patient must not have a systolic blood pressure less than 100 mmHg</i>

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AND
Clinical criteria:
Patient must receive concomitant standard chronic heart failure treatment, which must include: the maximum tolerated dose of a beta-blocker; AND mineralcorticoid receptor antagonist, unless contraindicated or not tolerated. 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
AND
Clinical criteria:
Patient must be receiving treatment with an ACE inhibitor, OR an angiotensin II antagonist (ARB), OR angiotensin receptor with neprilysin inhibitor (ARNi) combination therapy unless contraindicated or not be tolerated
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,
AND
Population criteria:
Patient must be aged 18 years or older.
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: The date of the decompensation event and date of initiation of treatment with this drug must be documented in the patient's medical records when PBS-subsidised treatment is initiated.
Treatment Phase: Continuing treatment
Restriction type: <input checked="" type="checkbox"/> Authority Required (Streamlined) [new code]
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
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
AND
Clinical criteria:
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,
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.

- 3.2 The proposed clinical criteria are less specific than the VICTORIA trial eligibility criteria:
- A time frame for identifying the recent decompensation event was not identified. The ESC and PBAC considered that a time frame should be specified in the restriction consistent with the VICTORIA trial, which required patients to have had a heart failure hospitalisation in the past 6 months or intravenous diuretic therapy for heart failure (without hospitalisation) in the past 3 months. Further, the ESC and the PBAC considered that a prescribing instruction should be included specifying that the date of the decompensation event and date of initiation of treatment be recorded in the patient's medical records.
 - Assessment of NT-proBNP levels as a proxy for stabilisation following hospitalisation and prior to initiation of vericiguat was not specified. The VICTORIA trial required patients in sinus rhythm to have NT-proBNP ≥ 1000 pg/mL or BNP ≥ 300 pg/mL; and patients in atrial fibrillation to have NT-proBNP ≥ 1600 pg/mL or BNP ≥ 500 pg/mL.
 - Criteria to identify stabilised patients were not included. The VICTORIA trial excluded patients who were unstable, defined as patients receiving IV treatment in the 24 hours prior to randomisation; and/or a systolic blood pressure < 100 mmHg. The ESC considered that criteria around recent use of IV therapy or recent blood pressure stability may not be required if initiation of vericiguat were limited to cardiologists (or under the supervision of a cardiologist). However, the PBAC considered that it would be appropriate for the restriction to specify that the patient: must not have required IV treatment within the previous 24 hours; should not be haemodynamically unstable (e.g. must not have a systolic blood pressure less than 100 mmHg); and must not have evidence of fluid overload.
- 3.3 The proposed PBS restriction does not align with the population modelled in the economic evaluation, which excluded patients in the highest quartile of NT-proBNP from the VICTORIA trial (NT-proBNP > 5314 pg/mL). The submission claimed that an NT-proBNP requirement in the proposed restriction may inappropriately restrict access to vericiguat treatment due to the limited use of NT-proBNP testing and lack of MBS reimbursement. See section 4 below for further discussion regarding this.
- 3.4 The submission suggested that the assessment of stability should be considered in its entirety through clinical assessment of optimised diuretic therapy, volume status and other heart failure therapies. The Pre-Sub-Committee Response (PSCR) argued that the NT-proBNP Q1-Q3 subgroup is a proxy for identifying stabilised patients. However, the ESC noted that the VICTORIA trial excluded patients who were considered clinically unstable at baseline (i.e. received IV therapy in the 24 hours prior to randomisation and/or had a systolic blood pressure < 100 mmHg), but still included 1,201/5,050 patients (24%) with a NT-proBNP $> 5,314$ pg/mL, and 672/4,805 (14%) with a NT-proBNP $> 8,000$ pg/mL. The ESC considered that the proposed restriction is likely to include patients with very high NT-proBNP levels who are likely to experience poorer

outcomes compared to patients treated with SoC alone (see Subgroup analyses section below).

- 3.5 The restriction positioned vericiguat as an add-on therapy to the following therapies unless contraindicated or not tolerated: (a) an ACE inhibitor (ACEi), an angiotensin II receptor blocker (ARB), or an angiotensin receptor with neprilysin inhibitor (ARNi) combination therapy; and (b) maximum tolerated doses of a beta-blocker; and (c) a mineralocorticoid receptor antagonist (MRA). However, the ESC and PBAC considered that the requirement for concomitant treatment with a MRA should be removed, along with the titration requirements for beta-blocker therapy. This was consistent with the Committee's previous advice, in the context of sacubitril + valsartan that the requirement to be on a 'maximum tolerated dose' of a beta-blocker may complicate the management of patients and may not be consistent with current guidelines (para 7.6, sacubitril + valsartan, Public Summary Document (PSD), November 2020 PBAC meeting).
- 3.6 The requested restriction provides for vericiguat to be used with or without prior or concurrent sodium-glucose cotransporter-2 inhibitor (SGLT2i) heart failure medicines. No guidance was provided for the use of vericiguat in combination with SGLT2i medicines (use in the VICTORIA trial was <5%, and this usage was associated with the treatment of type 2 diabetes). However, the ESC and PBAC considered that the restriction should not specifically prohibit this combination given its advice that initiation of vericiguat should be limited to specialist cardiologists.
- 3.7 The sponsor requested an Authority Required (Streamlined) listing, however the PBAC considered that an Authority Required (telephone/online PBS Authorities system) listing would be more appropriate for the initial listing given the relatively high-risk population (who are required to have had a recent acute decompensation event and be on multiple concomitant medicines) and noting the Product Information states that vericiguat should be initiated under the supervision of a cardiologist. The sponsor accepted this change in the pre-PBAC response.
- 3.8 The ESC and PBAC considered that the restriction should require initiation under the supervision of specialist cardiologists. The sponsor accepted this change in the pre-PBAC response.
- 3.9 The submission stated that a patient access program was planned, but that a grandfathering restriction (to allow transition to PBS subsidy) was not required as the program criteria would be expected to align with the proposed PBS restriction. However, the PBAC considered that a grandfather restriction would be required to ensure that, at initiation of therapy, patients met the PBS criteria around experiencing a recent decompensation event and being euvolaemic.

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

4 Population and disease

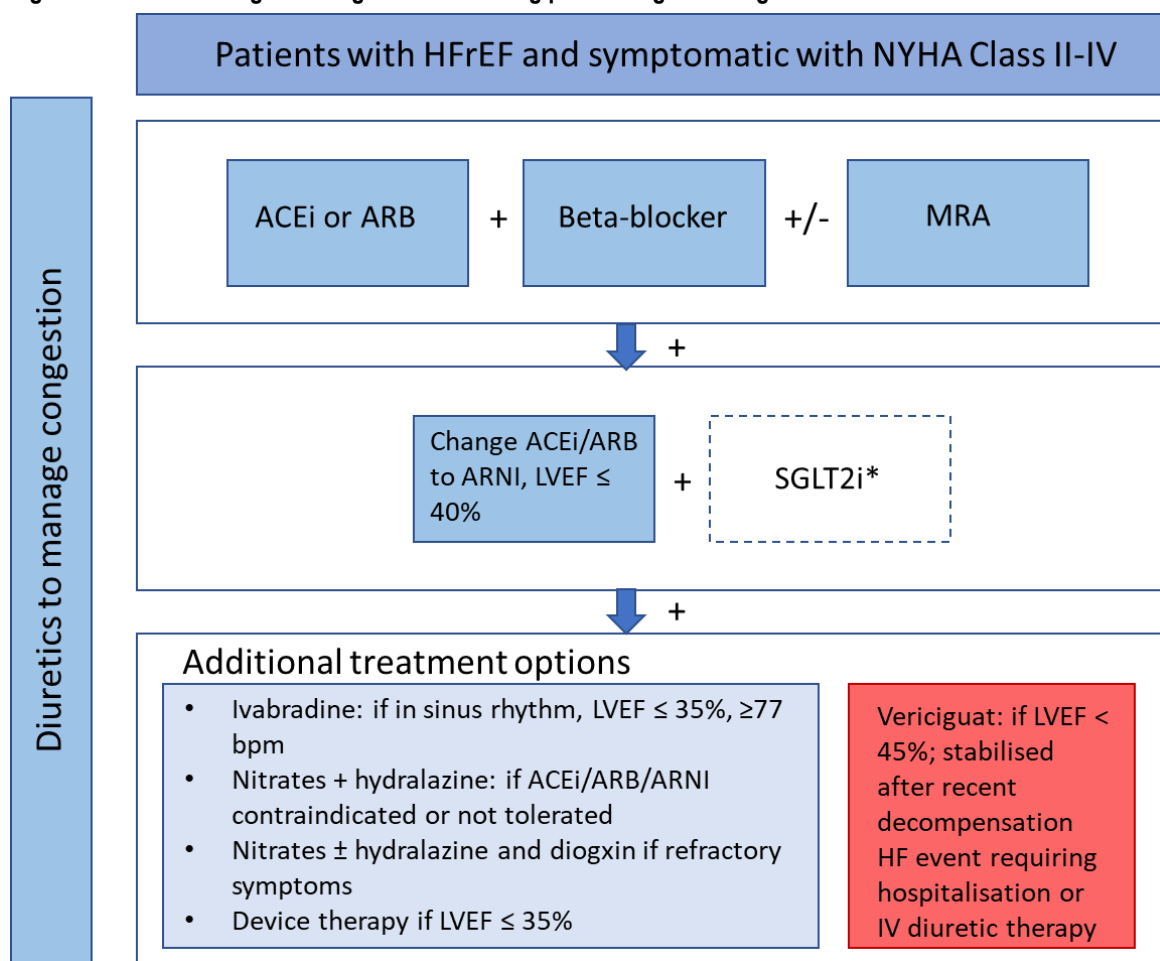
- 4.1 Chronic heart failure is a complex clinical syndrome characterised by symptoms such as dyspnoea, peripheral oedema and fatigue, caused by an underlying structural and/or functional cardiac abnormality that impairs the ability of the heart ventricle to fill with or eject blood. Common causes of heart failure include ischaemic heart disease, valvular heart disease, cardiomyopathies, hypertension, arrhythmias, and diabetes.
- 4.2 Heart failure is commonly classified based on the left ventricular ejection fraction (LVEF). Heart failure with reduced ejection fraction (HFrEF) refers to symptoms with or without signs of heart failure and a left ventricular ejection fraction $\leq 40\%$. If LVEF is mildly reduced (41-49%), often called heart failure with mildly reduced ejection fraction (HFmrEF), additional criteria are required for diagnosis (signs of heart failure, diastolic dysfunction with high filling pressure demonstrated by invasive means or echocardiography or biomarker testing).
- 4.3 Vericiguat is a novel, orally administered, soluble guanylate cyclase stimulator which enhances the cyclic guanosine monophosphate (GMP) pathway important for both myocardial and vascular function.
- 4.4 Acute decompensated heart failure (ADHF) results from a variety of etiological pathways (e.g. coronary artery disease, cardiac arrhythmias including atrial fibrillation, myocarditis, acute or progressive valve disease, cardiomyopathy, hypertension), and precipitant factors (infection, non-adherence to treatment regimens, diet and lifestyle changes), or with no identified precipitating cause. Monitoring changes in cardiac congestion following treatment for ADHF reduces the risk of re-hospitalisation related to residual congestion at discharge (Girerd et al. 2018), and should include monitoring of clinical symptoms, biological biomarkers (e.g. BNP and NT-proBNP), echocardiography and other radiological investigations.
- 4.5 BNP and NT-proBNP are useful diagnostic tools to rule out heart failure in patients with undifferentiated dyspnoea (Girerd et al. 2018; Atherton et al. 2018), have demonstrated strong prognostic predictive value in heart failure and are powerful independent predictors of mortality and adverse cardiovascular events including hospitalisation (Januzzi et al. 2006; Lam et al. 2010). However, BNP and NT-proBNP peptide levels generally increase with age, renal impairment, cardiac arrhythmias (atrial fibrillation), may be reduced in obesity (Atherton et al. 2018; Das et al. 2005), may be impacted by the use and titration of heart failure medicines (e.g. beta blockers, ARNi; Atherton et al. 2018) and have shown uncertain predictive value in assessing stabilisation after a ADHF events.
- 4.6 The European Society of Cardiology (ESC) 2021 Guidelines for the diagnosis and treatment of acute and chronic heart failure (McDonagh et al., 2021) suggest that a

pre-discharge NT-proBNP be considered in patients with suspected residual congestion after an ADHF event. However, given the cost of BNP and NT-proBNP peptide assays, the prolonged half-life of NT-proBNP, and the uncertainty of its predictive value in assessing patient stabilisation after ADHF events, the use of NT-proBNP in patient management is not recommended in the current NHFA/CSANZ 2018 heart failure management guidelines (Atherton et al. 2018). The South Australian retrospective virtual registry study (Chew et al. 2021) confirmed that NT-proBNP testing is not routinely used in Australian clinical practice.

- 4.7 The commentary and the ESC considered that stabilisation or instability after an ADHF event was not adequately defined in the submission. Notwithstanding the exclusion of patients showing haemodynamic instability at randomisation in the VICTORIA trial, the submission used the threshold of the baseline NT-proBNP quartile 4 (i.e. NT-proBNP Q1-Q3 or NT-proBNP ≤ 5314 pg/mL) from the VICTORIA trial as a proxy for 'stabilised' patients. While NT-proBNP is a valuable diagnostic and risk assessment tool in heart failure management, its use as an indicator of heart failure stabilisation after a decompensation event requiring hospitalisation or intravenous diuretic therapy has not been validated.
- 4.8 The ESC noted that while NT-proBNP is currently MBS listed (Item 66830, which is for 'quantitation of BNP or NT-proBNP for the diagnosis of heart failure in patients presenting with dyspnoea to a hospital Emergency Department'), this listing is for a purpose unrelated to the context of the VICTORIA study population for vericiguat. The ESC further noted that MSAC application 1689, considered by PASC in December 2021, was also for unrelated purposes (application 1689 is for patients with either systemic sclerosis (scleroderma) or previously diagnosed with pulmonary arterial hypertension)¹.
- 4.9 The ESC considered that a new integrated codependent submission would be required in order to assess vericiguat for the proposed post hoc subgroup and to have the prerequisite NT-proBNP test funded via the MBS. The ESC proposed that an alternative may be to use the results from the ITT population (rather than the NT-proBNP Q1-Q3 subgroup) in the economic model.
- 4.10 The recommended starting dose of vericiguat is 2.5 mg orally once daily, up-titrated at 14 day intervals to 5 mg and then 10 mg once daily (maximum target dose) as tolerated. Vericiguat would be administered as an add-on to standard of care (SoC) heart failure therapies after stabilisation of the patient's condition following a decompensation heart failure event.
- 4.11 Figure 1 outlines the clinical management algorithm proposed in the submission.

¹ <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1689-public>

Figure 1: Clinical management algorithm indicating positioning of vericiguat if listed on the PBS



Source: Figure 1-8, p47 of the submission

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association classification; SGLT2i, sodium-glucose transport protein 2 inhibitor

* SGLT2i therapies not currently PBS listed

4.12 The submission proposed that vericiguat would be positioned after four other therapies (ACEi/ARB/ARNI, beta-blocker, potentially a MRA, and SGLT2 inhibitors) and also after diuretics.

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

5 Comparator

5.1 The submission nominated placebo plus SoC (including ACEi/ARBs or ARNis, beta-blockers, MRAs, and diuretics) as the main comparator, consistent with clinical guidelines and expert opinion provided to the sponsor. The ESC considered this was appropriate.

- 5.2 The submission acknowledged that the SGLT2 inhibitors dapagliflozin and empagliflozin were recently considered and recommended by the PBAC for the treatment of HFrEF. The clinical management algorithm positioned vericiguat as an add-on to SoC heart failure therapies (including SGLT2 inhibitors), but it is unclear whether vericiguat will be used as an add-on or alternative to SGLT2 inhibitors. The ESC advised the role of vericiguat alongside SGLT2 inhibitors was not clear, but it was likely SGLT2 inhibitors will be used as SoC, prior to vericiguat.

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 the clinical need for vericiguat given it has a different mechanism of action to current therapies and has neutral renal and haemodynamic effects. The clinician considered that the most appropriate place in therapy for vericiguat would be in patients: with a recent hospitalisation for heart failure or recent use of IV diuretics; who remain symptomatic despite being on guideline-directed therapy with ACE/ARB/ARNi, beta-blocker, MRA and SGLT2 inhibitors; with systolic blood pressure greater than 100 mm Hg; NYHA class II/III heart failure; who are mobile but have problems with usual activities; and who have shortness of breath with mild to moderate exertion. The clinician outlined that vericiguat would be of little clinical value in patients who are unstable, for example those: with systolic blood pressure less than 100 mm Hg; who have had recurrent admissions to hospital in a short period of time despite guideline-directed treatment; and/or who remain tachycardic with significant renal impairment and dyspnoea.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from an individual whose comments described the importance, to patients and their families, of access to therapies that may reduce the risk of re-hospitalisation.

Clinical trials

- 6.3 The submission was based on one head-to-head phase 3 randomised trial (VICTORIA) comparing vericiguat plus SoC to placebo plus SoC, and one supporting phase 2 dosing study (SOCRATES-Reduced) comparing three vericiguat dose strengths plus SoC to placebo plus SoC.
- 6.4 The economic evaluation was based on a post-hoc subgroup analysis of the VICTORIA trial primary and key secondary outcomes, including patients with baseline NT-proBNP levels in quartiles 1-3 (NT-proBNP Q1-Q3), as a proxy for stabilised patients.
- 6.5 Details of the trials presented in the submission are provided in the table below.

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Table 2: Trials presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
VICTORIA (MK-1242-001)	A randomized parallel-group, placebo-controlled, double-blind, event-driven, multi-center pivotal phase III clinical outcome trial of efficacy and safety of the oral sGC stimulator vericiguat in patients with heart failure with reduced ejection fraction (HFrEF) - Vericiguat global study in patients with heart failure with reduced ejection fraction (VICTORIA) Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in patients with heart failure and reduced ejection fraction; VICTORIA Study Group Lam CSP, Giczewska A, Sliwa K, et al. Clinical outcomes and response to vericiguat according to index heart failure event: Insights from the VICTORIA trial. VICTORIA Study Group Mentz RJ, Mulder H, Mosterd A, et al. Clinical outcome predictions for the vericiguat global study in patients with heart failure with reduced ejection fraction (VICTORIA) trial. VICTORIA Study Group Voors AA, Mulder H, Reyes E, et al. Renal function and the effects of vericiguat in patients with worsening heart failure with reduced ejection fraction: insights from the VICTORIA (Vericiguat Global Study in Patients with HFrEF) trial Ezekowitz JA, O'Connor CM, Troughton RW, et al. N-Terminal pro-B-type natriuretic peptide and clinical outcomes: Vericiguat heart failure with reduced ejection fraction study Pieske B, Patel MJ, Westerhout CM, et al. Baseline features of the VICTORIA (vericiguat global study in patients with heart failure with reduced ejection fraction) trial. VICTORIA Study Group	Clinical Study Report 4 March 2020 New England Journal of Medicine 2020; 382:1883-1893 JAMA Cardiology 2021; 6(6): 706-712. Journal of Cardiac Failure 2021; S1071-9164 (21) 00206-2 (online). European Journal of Heart Failure 2021; 23(8):1313-1321. JACC: Heart Failure 2020; 8(11):931-939. European Journal of Heart Failure 2019; 21(12):1596-1604.
SOCRATES-REDUCED	A randomized parallel-group, placebo-controlled, double-blind, multicenter dose finding phase II trial exploring the pharmacodynamic effects, safety and tolerability, and pharmacokinetics of four dose regimens of the oral sGC stimulator BAY 1021189 over 12 weeks in patients with worsening heart failure and reduced ejection fraction (HFrEF) - Soluble guanylate cyclase stimulator in heart failure patients with reduced EF (SOCRATES-REDUCED). Gheorghiu M, Greene SJ, Butler J, et al. Effect of vericiguat, a soluble guanylate cyclase stimulator, on natriuretic peptide levels in patients with worsening chronic heart failure and reduced ejection fraction: The SOCRATES-REDUCED randomized trial	Clinical Study Report 5 May 2021 JAMA 2015; 314(21):2251-62.

Source: Table 2-3, pp57-58 of the submission

6.6 The key features of the direct randomised trials included in the submission are summarised in the table below.

Table 3: Key features of the included trials

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in model
Vericiguat plus SoC versus placebo plus SoC						
VICTORIA	5050	Phase III, R, PC, DB, MC, Median follow-up 10.8 months	Low	<ul style="list-style-type: none"> Adults with HFrHF, NYHA class II-IV, LVEF <45% in prior 12 months Receiving SoC therapies HHF in prior 6 months or IV diuretics for HF in prior 3 months NT-proBNP ≥1000 pg/mL or BNP ≥300 pg/mL^a Excluded clinically unstable patients with IV therapy in the 24 hours prior to randomisation; and/or SBP <100 mmHg 	<ul style="list-style-type: none"> Composite of first event of CV death or HHF Time CV death, Time to HHF, Total hospitalisation, All-cause mortality, Composite of time to all-cause mortality or HHF, Change in KCCQ Change in EQ-5D-5L 	<ul style="list-style-type: none"> Post-hoc regression analysis of time to first hospitalisation and time to cardiovascular death in patients pre- and post-hospitalisation. Post-hoc analysis of EQ-5D scores
SOCRATES-Reduced	456	Phase IIb dosing study, R, PC, DB, MC, Duration of 12 weeks	Low	<ul style="list-style-type: none"> Adults with HFrHF, NYHA class II-IV, LVEF <45% Receiving SoC therapies Worsening HF at hospitalisation or IV diuretics for HF, defined by NT-proBNP ≥1000 pg/mL or BNP ≥300 pg/mL^a Receiving SoC therapies Clinically stabilised defined as no IV vasodilator for >24 hours and no IV diuretic for >12 hours before randomisation, and SBP ≥110 to <160 mmHg and resting HR ≥50 to <100 beats per minute at randomisation 	<ul style="list-style-type: none"> Change from baseline in log-transformed NT-proBNP Time to all-cause mortality, Time to CV death, Time to HHF, Composite of time to CV death or HHF 	Not used

Source: Table 2-5, pp66-67 of the submission

Abbreviations: BNP, B-type natriuretic peptide; CV, cardiovascular; DB, double blind; EQ-5D-3L, EuroQoL- 5-dimension 5-level questionnaire; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalisation for heart failure; HR, heart rate; IV, intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MC, multi-centre; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; NYHA, New York Heart Association; PC, placebo controlled; R, randomised; SBP, systolic blood pressure; SoC, standard of care

^a Patients in atrial fibrillation - BNP ≥500 pg/mL or NT-proBNP ≥1600 pg/mL

6.7 The VICTORIA trial compared vericiguat plus SoC to placebo plus SoC in patients with HFrEF (NYHA class II-IV, LVEF <45%) stabilised after a recent hospitalisation for heart failure in the prior 6 months, or after outpatient intravenous diuretic therapy for heart failure in the prior 3 months, with raised serum NT-proBNP or BNP levels indicative of an acute or deteriorating heart failure event and prior treatment with standard of care heart failure therapies. The ESC and the PBAC considered the entry criteria of LVEF <45% was unusual given clinical trials in HFrEF generally use thresholds of ≤40%. The use of the higher threshold would have led to the enrolment of a number of patients with HFmrEF.

- 6.8 The submission acknowledged differences between the VICTORIA trial and the Australian setting in terms of age (68 years in the VICTORIA trial versus 81 years in Chew 2021 cohort with recent HHF), sex (male 76.1% in the VICTORIA trial versus 53.8% in the Chew 2021 cohort with recent HHF), baseline NT-proBNP (median 2,816 pg/mL versus 5,367pg/mL), and SoC pharmacotherapy use (e.g. ARNi use 14.5% versus 42%), but argued that the differences are unlikely to have an effect on outcomes with vericiguat treatment, as pre-specified subgroup analyses and a post-hoc multivariate Patient Response Identifiers for Stratified Medicine (PRISM) analysis showed no treatment effect interaction for any patient characteristics other than baseline NT-proBNP. However, the observed differences in patient characteristics may reflect differences in baseline risk between the trial population and Australian setting and may result in differences in the absolute benefit of vericiguat. Further, the PBAC noted that, compared with the VICTORIA trial population, the likely PBS population may have poorer renal function (median eGFR of 58.4 mL/min/1.73m² in the VICTORIA trial versus 44.0 mL/min/1.73m² in the Chew 2021 cohort with recent HHF) and higher rates of use of MRA therapies (70.3% versus 83%, respectively).
- 6.9 The submission argued that differences in the use of ACEi/ARB and ARNi heart failure medicines between the VICTORIA trial and the Australian setting reflect the evolving treatment landscape for HFrEF therapies, with sacubitril/valsartan PBS listed in July 2017 and SGLT2i heart failure medicines recommended for listing by the PBAC in September and November 2021. The impact of differences in SoC between the VICTORIA trial and the Australian setting, and the use of vericiguat in combination with SGLT2i heart failure medicines is unclear, and the ESC considered that these differences were likely to impact the absolute benefit of vericiguat in the Australian setting.

Comparative effectiveness

Subgroup analyses

- 6.10 Tests for treatment effect interaction indicated a significant interaction by baseline NT-proBNP quartile, with vericiguat associated with no beneficial effect in the quartile 4 subgroup (NT-proBNP Q4) with baseline NT-proBNP >5314 pg/mL (as shown in Table 4, the HR for the composite of CV death or hospitalisation for heart failure was 1.15 (95% CI: 0.99, 1.34) in this subgroup); and a significant interaction by baseline age, with vericiguat being associated with a smaller magnitude of effect in patients aged ≥75 years.

Table 4: Time to first event of cardiovascular death or heart failure hospitalisation (VICTORIA; ITT; CEC)

Outcome	Vericiguat + SoC	Placebo + SoC	Hazard ratio (95% CI)
ITT population			
N	2526	2524	
Composite of CV death or HHF n (%)	897 (35.5%)	972 (38.5%)	0.90 (0.82, 0.98)
• HHF first event n (%)	691 (27.4%)	747 (29.6%)	-
• CV death first event n (%)	206 (8.2%)	225 (8.9%)	-
Time to CV death n (%)	414 (16.4%)	441 (17.5%)	0.93 (0.81, 1.06)
Time to first HHF event n (%)	691 (27.4%)	747 (29.6%)	0.90 (0.81, 1.00)
Baseline NT-proBNP ≤5314 pg/mL (Q1-Q3) subgroup			
N	1798	1806	
Composite of CV death or HHF n (%)	506 (28.1%)	619 (34.3%)	0.78 (0.69, 0.88)
• HHF first event n (%)	406 (22.6%)	504 (27.9%)	-
• CV death first event n (%)	100 (5.6%)	115 (6.4%)	-
Time to CV death n (%)	190 (10.6%)	240 (13.3%)	0.78 (0.65, 0.94)
Time to first HHF event n (%)	406 (22.6%)	504 (27.9%)	0.77 (0.67, 0.88)
Baseline NT-proBNP >5314 pg/mL (Q4) subgroup			
N	616	585	
Composite of CV death or HHF n (%)	355 (57.6%)	302 (51.6%)	1.15 (0.99, 1.34)
• HHF first event n (%)	251 (40.7%)	209 (35.7%)	-
• CV death first event n (%)	104 (16.9%)	93 (15.9%)	-
Time to CV death n (%)	208 (33.8%)	169 (28.9%)	1.16 (0.95, 1.43)
Time to first HHF event n (%)	251 (40.7%)	209 (35.7%)	1.19 (0.99, 1.44)

Source: Table 2-38, p133 of the submission; Tables 2.5.1 and 2.5.2 of the commentary

Abbreviations: CV, cardiovascular; HHF, hospitalisation for heart failure; ITT, intention-to-treat; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SoC, standard of care

Note: Cut-off points for NT-proBNP quartiles were Q1 - ≤1556 pg/mL, Q2 - >1556 to ≤2816 pg/mL, Q3 - >2816 to ≤5314 pg/mL, and Q4 - >5314 pg/mL. Compared to the ITT population, 112 patients in the vericiguat treatment arm and 132 in the placebo arm were not included in the subgroup analysis

- 6.11 In the post-hoc subgroup analysis of the primary composite outcome, patients with a baseline NT-proBNP ≤5314 pg/mL (Q1-Q3) treated with vericiguat plus SoC showed a relative hazard reduction of 22% versus placebo plus SoC, a larger relative hazard reduction compared to the overall ITT population (10% reduction). Similar results were observed in the key secondary outcomes. The ESC noted the post-hoc subgroup analysis did not include a test for interaction or adjustment for multiplicity.
- 6.12 Patients with a baseline NT-proBNP >5314 pg/mL showed a relative hazard increase of 15%, with larger proportions of patients treated with vericiguat plus SoC reporting cardiovascular death or hospitalisation for heart failure compared to placebo plus SoC. A similar pattern was observed in the post-hoc subgroup analyses of the key secondary outcomes including cardiovascular death.
- 6.13 The submission suggested that patients with very high NT-proBNP (NT-proBNP Q4) in the VICTORIA trial were clinically unstable and therefore would not meet the criteria for vericiguat treatment in the proposed restriction. However, the VICTORIA trial defined clinically unstable patients as those who received IV therapy in the 24 hours prior to randomisation and/or a systolic blood pressure <100 mmHg). The ESC considered the NT-proBNP Q4 group was a higher risk subgroup who did not benefit

(and may have had worse outcomes), rather than just being a proxy for unstable patients. The submission considered that the NT-proBNP Q1-Q3 subgroup of the VICTORIA trial could be considered a proxy for the eligible population of patients stabilised following a recent heart failure decompensation event; and this subgroup formed the basis of the modelled economic evaluation.

- 6.14 Compared to the NT-proBNP Q1-Q3 subgroup, patients in the NT-proBNP Q4 subgroup of the VICTORIA trial were older, and larger proportions were randomised while hospitalised or within 3 months of hospitalisation, were NYHA class III/IV, and had lower LVEF and eGFR. In addition, lower proportions of patients in the NT-proBNP Q4 subgroup were receiving treatment with ACEi/ARB (Q1-Q3 75.5%; Q4 68.5%), ARNi (14.6%; 13.3%), beta-blockers (93.5%, 91.8%), MRA (72.7%; 64.3%) or triple combination therapy (62.9%; 50.7%) as SoC. These differences between the NT-proBNP Q1-Q3 versus Q4 subgroups suggest that patients in the NT-proBNP Q4 subgroup experienced more severe heart failure symptoms. However, it is unclear if these differences were due to delayed stabilisation after a decompensated heart failure event, lower tolerated doses of SoC pharmacotherapy, or other factors. The ESC considered that it was also unclear how this population could be identified with any certainty a priori without measurement of NT-proBNP.
- 6.15 The TGA and EMA noted that vericiguat generally performed worse in more fragile patient populations (eGFR ≤ 30 ml/min/1.73 m² and LVEF ≥ 40 to $< 45\%$). Overall, the ESC considered that it was unclear whether 'more fragile' patients would have a lower incremental treatment effect with vericiguat given that no statistically significant treatment effect interactions were observed for these variables and, further, LVEF $\geq 40\%$ is not generally considered a proxy for more fragile patients (lower LVEF is generally associated with higher mortality). The submission argued that a post-hoc PRISM analysis only identified NT-proBNP as the most influential predictor of treatment response, whereas age, ejection fraction, and eGFR were not. No details of the PRISM analysis were provided with the submission and the results of the analysis could not be verified. The PSCR stated that the PRISM analysis was a general-purpose subgroup identification approach used to understand the independent influence of baseline characteristics on treatment effect when considered simultaneously in the same algorithm. The PSCR stated that 64 baseline variables were included in this model, and presented an illustration of the PRISM algorithm used. However, the full analysis was not presented and could not be evaluated.

ITT population

- 6.16 The table below summarises the results of the primary composite outcome of time to first cardiovascular death or hospitalisation for heart failure, of the VICTORIA trial.

Table 5: Time to first event of cardiovascular death or heart failure hospitalisation (VICTORIA; ITT; CEC)

Outcome	Vericiguat + SoC N=2526	Placebo + SoC N=2524	Hazard ratio (95% CI)
Composite of time to CV death or HHF n (%)	897 (35.5%)	972 (38.5%)	0.90 (0.82, 0.98)
• HHF first event n (%)	691 (27.4%)	747 (29.6%)	-
• CV death first event n (%)	206 (8.2%)	225 (8.9%)	-
Median duration of follow-up	10.8 months		-

Source: Table 2-23, p104 of the submission

Abbreviations: CEC, Clinical Endpoint Committee; CV, cardiovascular; HHF, hospitalisation for heart failure; ITT, intention-to-treat; SoC, standard of care

6.17 Patients treated with vericiguat plus SoC showed a statistically significant improvement in the primary composite outcome of time to cardiovascular death, or hospitalisation for heart failure compared to placebo plus SoC, with a 10% relative hazard reduction over a median duration of follow-up of 10.8 months. The difference in absolute risk between treatment arms was low and primarily driven by differences in the rates of hospitalisation for heart failure.

6.18 The table below summarises the results of the key secondary outcomes of the VICTORIA trial (ITT).

Table 6: Results of the key secondary outcomes of cardiovascular death, hospitalisation for heart failure, all-cause mortality and the composite of time to all-cause mortality or HHF (VICTORIA; ITT; CEC)

Outcome	Vericiguat + SoC N=2526	Placebo + SoC N=2524	Hazard ratio (95% CI)
CV death n (%)	414 (16.4%)	441 (17.5%)	0.93 (0.81, 1.06)
• Heart failure	165 (6.5%)	191 (7.6%)	-
• Myocardial infarction	10 (0.4%)	11 (0.4%)	-
• Stroke	7 (0.3%)	16 (0.6)	-
• Other cardiovascular event	13 (0.5%)	9 (0.4%)	-
• Sudden cardiac death	107 (4.2%)	113 (4.5%)	-
• Undetermined cause of death	112 (4.4%)	101 (4.0%)	-
Composite of time to all-cause mortality or HHF n (%)	957 (37.8%)	1032 (40.9%)	0.90 (0.83, 0.98)
All-cause mortality n (%)	512 (20.3%)	534 (21.2%)	0.95 (0.84, 1.07)
HHF n (%)	691 (27.4%)	747 (29.6%)	0.90 (0.81, 1.00)

Source: Table 2-24, p106 of the submission

Abbreviations: CEC, Clinical Endpoint Committee; CI, confidence interval; CV, cardiovascular; HHF, hospitalisation for heart failure; ITT, intention to treat; SoC, standard of care

6.19 There was no statistically significant difference in the rate of cardiovascular death or all-cause mortality between patients treated with vericiguat plus SoC compared to placebo plus SoC. Patients treated with vericiguat plus SoC showed a statistically significant improvement in the secondary composite outcome of time to all-cause mortality, or hospitalisation for heart failure compared to placebo plus SoC. As with the primary composite outcome, the difference in absolute risk between treatment arms was primarily driven by differences in the rates of hospitalisation for heart failure.

6.20 The table below summarises the results of the EQ-5D-5L questionnaire for the index and VAS scores in the VICTORIA trial (ITT).

Table 7: Change from baseline in EQ-5D-5L UK index and VAS scores at week 32 (VICTORIA; ITT; exploratory)

Outcome	Baseline		Week 32		Difference LS mean (95% CI)
	N	LS mean (SD)	N	LS mean (SD)	
EQ-5D-5L index score					
Vericiguat + SoC	2378	0.69 (0.24)	2021	0.58 (0.49)	-0.12 (-0.14, -0.10)
Placebo + SoC	2345	0.69 (0.23)	2009	0.55 (0.51)	-0.13 (-0.15, -0.11)
Vericiguat versus placebo - LS means (95% CI)					0.01 (-0.01, 0.04)
EQ-5D-5L VAS score					
Vericiguat + SoC	2378	64.4 (18.9)	2021	61.3 (28.6)	-3.3 (-4.5, -2.2)
Placebo + SoC	2345	64.0 (18.4)	2009	59.9 (29.5)	-3.8 (-4.9, -2.6)
Vericiguat versus placebo - LS means (95% CI)					0.4 (-1.2, 2.1)

Source: Table 2-29, p113 of the submission; Table 11-17, p147 and Table 14.2-71, p1009 of the VICTORIA Clinical Study Report
 Abbreviations: EQ-5D-5L, EuroQoL- 5-dimension 5 level questionnaire; ITT, intention-to-treat; LS: Least Square; SD, standard deviation; SoC, standard of care; VAS, visual analog scale

Note: Deaths assigned worst possible score for all post-death visits up to primary completion date (18 June 2019)

- 6.21 Changes from baseline in EQ-5D-5L index and VAS scores were similar between treatment arms, with no statistically significant differences in EQ-5D-5L index and VAS scores between patients treated with vericiguat plus SoC compared to placebo plus SoC.
- 6.22 Similarly, results of the KCCQ clinical summary score, overall summary score and total symptom score for change from baseline to 32 weeks in the Victoria trial (ITT) showed no statistically significant differences in mean change from baseline KCCQ summary scores between patients treated with vericiguat plus SoC and placebo plus SoC.

Comparative harms

- 6.23 The table below summarises the results of the key safety outcomes for the VICTORIA trial comparing vericiguat plus SoC with placebo plus SoC.

Table 8: Summary of adverse events in the VICTORIA trial (all patients as treated)

Adverse events n (%)	Vericiguat + SoC N=2519	Placebo + SoC N=2515
At least one adverse event	2027 (80.5%)	2036 (81.0%)
Any drug-related adverse event	367 (14.6%)	294 (11.7%)
Any serious adverse event	826 (32.8%)	876 (34.8%)
Any serious drug-related adverse event	30 (1.2%)	20 (0.8%)
Discontinuation - any adverse event	167 (6.6%)	158 (6.3%)
Discontinuation - serious adverse event	71 (2.8%)	87 (3.5%)
Any adverse event resulting in death	83 (3.3%)	85 (3.4%)
Serious adverse events reported by ≥2% of patients		
Any serious AE	826 (32.8%)	876 (34.8%)
Infections and infestations	269 (10.7%)	270 (10.7%)
Pneumonia	101 (4.0%)	112 (4.5%)
Cardiac disorders	203 (8.1%)	269 (10.7%)
Cardiac failure	80 (3.2%)	110 (4.4%)
Renal and urinary disorders	141 (5.6%)	133 (5.3%)
Acute kidney injury	64 (2.5%)	51 (2.0%)
Gastrointestinal disorders	100 (4.0%)	92 (3.7%)
Respiratory, thoracic and mediastinal disorders	88 (3.5%)	90 (3.6%)
Nervous system disorders	82 (3.3%)	83 (3.3%)
Vascular disorders	81 (3.2%)	86 (3.4%)
Injury, poisoning and complications	65 (2.6%)	78 (3.1%)
Blood and lymphatic system disorders	53 (2.1%)	29 (1.2%)
Neoplasms	50 (2.0%)	48 (1.9%)
Treatment emergent adverse events of special interest		
Hypotension	388 (15.4%)	354 (14.1%)
Symptomatic hypotension	229 (9.1%)	198 (7.9%)
Syncope	101 (4.0%)	87 (3.5%)

Source: Table 2-32, pp116-117 of the submission and Table 2-34, p120 of the submission

Abbreviations: SoC, standard of care

- 6.24 The ESC noted that more patients experienced a drug-related adverse event with vericiguat plus SoC versus placebo plus SoC (14.6% versus 11.7%, respectively), but fewer experienced a serious adverse event (32.8% versus 34.8%) likely due to the reduction in heart failure observed.
- 6.25 The most frequently reported serious adverse events by system organ class were infections and infestations (10.7% both arms), cardiac disorders including heart failure (vericiguat 8.1%; placebo 10.7%) and renal and urinary disorders (vericiguat 5.6%; placebo 5.3%) including acute kidney injury (vericiguat 2.5%; placebo 2.0%).
- 6.26 The adverse events of clinical interest of symptomatic hypotension and syncope were more frequently reported in the vericiguat plus SoC treatment arm compared to placebo plus SoC (hypotension 15.4% vs 14.1%; syncope 4.0% vs 3.5%). Similarly, larger proportions of patients treated with vericiguat plus SoC compared to placebo plus SoC reduced or interrupted treatment (23.2% vs 21.8%) or discontinued treatment due to hypotension (1.9% vs 1.3%).

Benefits/harms

- 6.27 Based on the VICTORIA trial (ITT population), for every 100 patients treated with vericiguat plus SoC in comparison with placebo plus SoC over a median follow-up of 10.8 months:
- Approximately 3 fewer patients would experience a first event of hospitalisation for heart failure or death due to cardiovascular causes.
 - There would be no difference in cardiovascular death.
 - Approximately 2 fewer patients would experience hospitalisation due to heart failure.
 - Approximately 1 additional patient would experience symptomatic hypotension.

Clinical claim

- 6.28 The submission described vericiguat plus SoC as superior in terms of effectiveness compared with placebo plus SoC and comparable in terms of safety. This claim was reasonable.
- 6.29 The evaluation and the ESC considered that the magnitude of the treatment effect may be overestimated given:
- The magnitude of benefit associated with vericiguat plus SoC in the VICTORIA ITT population was small and primarily driven by differences in the rate of hospitalisation for heart failure. The minimal duration of follow-up, at 10.8 months, was short for a therapy intended for chronic usage. While the magnitude of the vericiguat treatment effect was larger in the post-hoc Q1-3 quartile NT-proBNP subgroups, it would be difficult to adequately identify this population in clinical practice, given NT-proBNP is not routinely measured in Australian clinical practice (and NT-proBNP is not reimbursed by the MBS for this indication).
 - Subgroup analyses demonstrated that NT-proBNP and age were treatment effect modifiers, with worse outcomes experienced in patients with higher NT-proBNP and older age. Given the differences between the Australian eligible population and the VICTORIA ITT and NT-proBNP subgroup populations in terms of NT-proBNP, age, gender, LVEF and eGFR, which suggest that the PBS population may include patients with more severe disease who may not achieve the same (small) benefits associated with vericiguat observed in the VICTORIA trial.
 - The estimated treatment effects were based on a population with less use of ARNi therapies (sacubitril/valsartan) and limited exposure to SGLT2i heart failure medicines; which is no longer reflective of clinical guidelines. The magnitude of benefit associated with the addition of vericiguat to standard therapy including SGLT2 inhibitors is unknown.
- 6.30 The PBAC considered that the claim of superior comparative effectiveness was reasonable although the magnitude of the treatment effect was modest and may have been overestimated in the trial.

- 6.31 The PBAC considered that the claim of comparable safety was likely reasonable but noted that vericiguat was associated with a slight increase in drug-related adverse events compared with placebo (14.6% versus 11.7%, respectively). Overall, the PBAC considered that vericiguat appeared to be reasonably well tolerated.

Economic analysis

- 6.32 The submission presented a stepped economic evaluation of vericiguat plus SoC versus SoC. The base case of the economic model relied on the NT-proBNP Q1-Q3 subgroup of the VICTORIA trial (patients with NT-proBNP ≤ 5314 pg/mL), which the submission suggested was a proxy for patients who have stabilised after a worsening event. As noted earlier, the ESC considered that the proposed subgroup population can only reliably be identified by measurement of NT-proBNP, which is not currently MBS-funded for the required purpose. The economic evaluation was presented as a cost utility analysis.

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Table 9: Key components of the economic evaluation

Component	Description
Treatments	Vericiguat plus standard of care versus standard of care alone (including ACE inhibitors/ARBs or ARNIs, beta blockers, mineralocorticoid receptor antagonists, and diuretics).
Time horizon	10 years in the model base case, versus 10.8 months median follow-up for the primary outcome in the VICTORIA trial.
Outcomes	Life years; quality adjusted life years (QALYs)
Methods used to generate results	Markov state transition model
Health states	No hospitalisation First HF hospitalisation event Post-first HF hospitalisation Subsequent HF hospitalisation Post-subsequent HF hospitalisation CV death Non-CV death
Cycle length	Monthly; half-cycle correction applied
Transition probabilities	Probabilities of hospitalisation and cardiovascular death pre- and post-hospitalisation based on post-hoc regression analyses of the VICTORIA trial ITT population. Parametric models were fitted to Kaplan Meier curves derived from the regression analyses, extrapolated to 10 years. The model generates survival curves for the NT-proBNP Q1-Q3 subgroup based on the baseline patient characteristics in the subgroup population. Cardiovascular death during hospitalisation based on the case fatality rate in the pooled vericiguat and placebo arms in the ITT population of the VICTORIA trial. Non-CV mortality based on Australian life tables (ABS 2020), adjusted to remove CV deaths (based on AIHW 2020 and ABS 2021 data).
Costs	The cost of vericiguat was based on the proposed DPMQ and 100% adherence and persistence. The cost of standard of care was based on the distribution of use of ACE inhibitors, beta-blockers, diuretics and MRAs at baseline in the ITT population of the VICTORIA trial; assumed daily doses; published DPMQs; and 100% adherence and persistence. Disease management costs were based on a survey of Australian cardiologists used to inform frequency of health professional visits; assumed proportions of patients seeing GPs, cardiologists and other physicians; and MBS fees. Heart failure hospitalisation costs based on weighted average cost of heart failure AR-DRGs (2018-2019) inflated to 2021 prices using the CPI for medical and hospital services. Terminal care costs based on the AR-DRG for heart failure admission of major complexity (F62C; 2018-2019) inflated to 2021 prices using the CPI for medical and hospital services. Adverse event costs were not included in the model.
Health related quality of life	Health state utilities (alive, no hospitalisation; HF hospitalisation event; post HF hospitalisation event) were derived from EQ-5D-5L data from the VICTORIA trial, using a linear mixed effects model, and the UK value set. (The ESC noted that the UK EQ5D-5L value set was used, despite this no longer being recommended by NICE ² .) Separate utility estimates were derived for the ITT population and NT-proBNP Q1-Q3 subgroup, based on differences in baseline patient characteristics in the VICTORIA trial. Utility values were adjusted for age by applying an annual utility decrement based on the age coefficient in the linear mixed effects model. Adverse event disutilities were not included in the model.
Discount rate	5% for costs and benefits
Software package	Microsoft Excel 365

Source: Table 3-1, p148 ; and Section 3.3 to 3.6 of the submission

² <https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l>

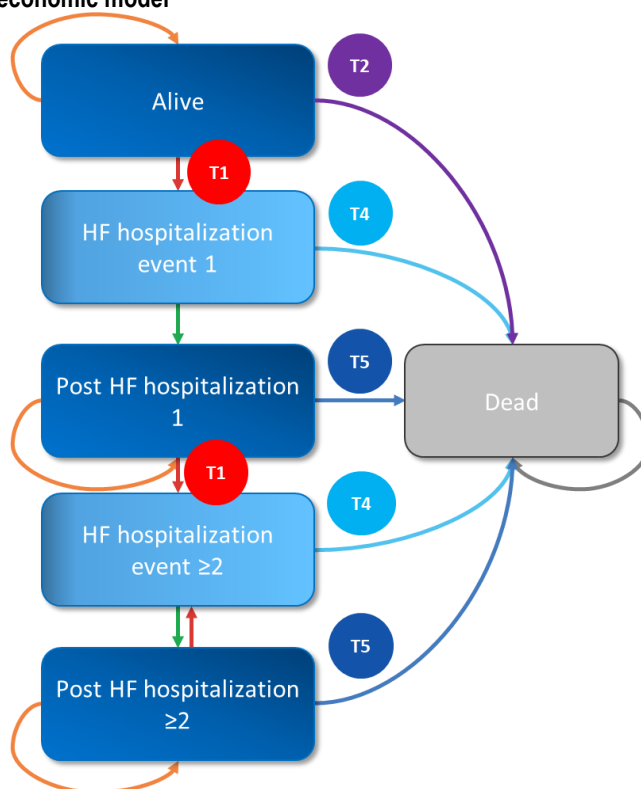
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Abbreviations: ACE, angiotensin-converting enzyme; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; ITT, intention to treat; LVEF, left ventricular ejection fraction; MRAs, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal-pro B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure

6.33 The submission nominated a 10-year time horizon, consistent with heart failure models previously considered by the PBAC for ivabradine and sacubitril/valsartan. In the model base case, 35-40% of patients remain alive at the end of the model (see model trace below), suggesting that a 10-year model may not be sufficient to capture the lifetime costs and consequences associated with vericiguat plus SoC. 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 10.8 months in the VICTORIA trial. The ESC noted that the vast majority of incremental costs (88.8%) and incremental QALYs (97.6%) are generated in the extrapolated period.

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

Figure 2: Structure of the economic model



Source: Figure 3-1, p161 of the submission

Abbreviations: HF, heart failure; T, transition

Notes: T1=hospitalisation rate (red arrows); T2=death rate pre-hospitalisation (purple arrow); T3=hospital discharge (green arrows); T4=case fatality rate of hospitalisation (light blue arrows); T5=death rate post-hospitalisation (dark blue arrows).

6.35 All patients begin in the alive (pre-hospitalisation) health state, stabilised after the index heart failure decompensation event. In each cycle, patients can experience a heart failure hospitalisation event, die of cardiovascular causes, or die of non-cardiovascular causes. Those who survive the hospitalisation event move to the post-hospitalisation health state after one cycle. Patients who have experienced a heart

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failure hospitalisation event have a higher risk of cardiovascular death than patients who are in the pre-hospitalisation state. Although additional health states are included for second and subsequent heart failure hospitalisation events (HF hospitalisation event ≥ 2 ; Post HF hospitalisation ≥ 2), the probability of a heart failure hospitalisation, and associated mortality, costs and quality of life are not affected by the number of prior hospitalisations.

6.36 Similar to the sacubitril/valsartan and dapagliflozin models previously considered by the PBAC (para 6.30, Sacubitril/valsartan, PSD, March 2016 PBAC meeting; para 6.21, Dapagliflozin PSD, July 2021 PBAC meeting), the vericiguat model is overly simplistic and does not incorporate health states that reflect the progressive nature of heart failure (such as by NYHA class or KCCQ quartiles), and the associated changes in costs, quality of life and mortality risk. The ESC considered that the simplistic structure introduces uncertainty and noted that the dapagliflozin models submitted to NICE and CADTH incorporated health states based on KCCQ-TSS and NYHA class. The ESC also noted when the PBAC recommended dapagliflozin it remained concerned that the model structure was not robust, however, at the reduced price the Committee was confident that the ICER would be in an acceptable range (\$15,000 to < \$25,000 per QALY gained) comparable to other treatments for chronic condition (para 7.7, Dapagliflozin PSD, September 2021 PBAC meeting).

6.37 The table below summarises the key drivers of the economic model.

Table 10: Key drivers of the model

Description	Method/Value	Impact
Curve fitting/internal validity Transition probabilities	<p>Probabilities of hospitalisation and cardiovascular death pre- and post-hospitalisation were based on post-hoc regression analyses of the VICTORIA trial ITT population. Parametric models were fitted to Kaplan Meier curves derived from the regression analyses, extrapolated to 10 years.</p> <p>The regression equations do not appear to generate estimates consistent with trial-based data, with modelled hospitalisation and cardiovascular death events underestimated compared to observed numbers of events in the ITT population of the VICTORIA trial over the average duration of follow-up (see table below). As the regression equations do not reliably predict observed outcomes within the trial period, the ESC considered they were unlikely to be sufficiently reliable to form the basis of further extrapolation over 10 years. The ESC also noted that the economic model does not use the observed time-to-event data in preference to the modelled data over the trial period as recommended in the PBAC Guidelines.</p> <p>The model traces indicate that the majority of benefit associated with vericiguat is derived from a reduction in cardiovascular mortality, which is inconsistent with the results of the primary outcome of the VICTORIA trial for the ITT analysis and NT-proBNP Q1-Q3 subgroup, which indicated that the difference in outcomes between treatment arms was primarily driven by differences in the rate of hospitalisation for heart failure.</p> <p>The vast majority of incremental costs (88.8%) and incremental QALYs (97.6%) are generated in the extrapolated period.</p>	High, favours vericiguat

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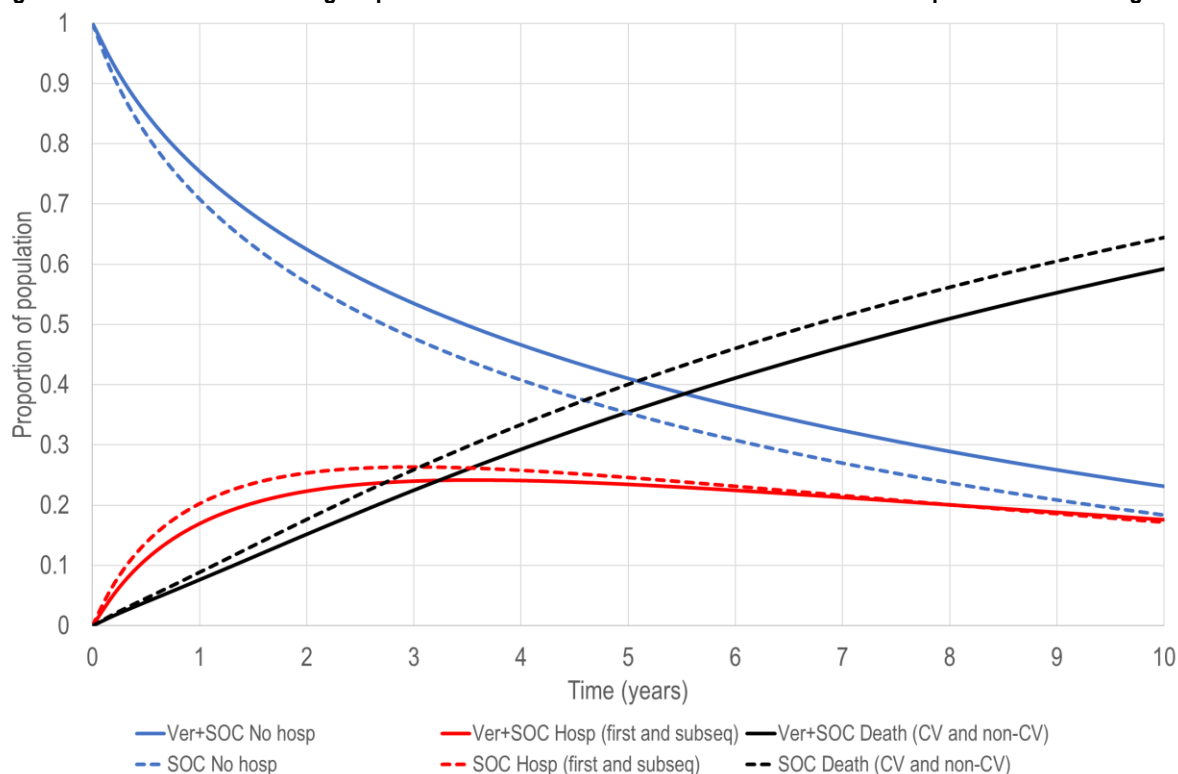
Description	Method/Value	Impact
Applicability of the modelled population and circumstances of use	There are concerns with the applicability of the modelled population, based on the VICTORIA trial NT-proBNP Q1-Q3 subgroup, to the PBS population given differences in risk factors of sex, LVEF and eGFR, and significant treatment effect interactions associated with baseline NT-proBNP and age, which may result in differences in the treatment benefit of vericiguat in the requested Australian population compared with the modelled population. There were differences in use of ARNi medicines between the trial and Australian setting (14.5% versus 42%) and the submission did not consider the recently recommended SGLT2 inhibitors, and the impact on vericiguat when used as an add on to standard of care which includes SGLT2 inhibitors. Further, the ESC considered that it was unreasonable to assume that the treatment outcomes and cost-effectiveness associated with vericiguat in the NT-proBNP Q1-Q3 subgroup of the VICTORIA trial will be realised in the Australian setting, without requiring measurement NT-proBNP.	High, favours vericiguat
Model structure	The structure of the economic model was similar to other models that the PBAC has previously considered were overly simplistic, as it does not incorporate health states that reflect the progressive nature of heart failure (such as by NYHA class or KCCQ quartiles), with associated changes in hospitalisation and mortality, costs and quality of life.	Unclear impact
Treatment persistence	The submission assumed perfect adherence and compliance to vericiguat and standard of care therapies over the 10 year duration of the model. This was inconsistent with assumptions used in the financial estimates, which assumed 42.9% discontinued treatment at 12 months (including deaths) and a fixed treatment duration of 14 months*. The approach used in the economic model will not reflect persistence in clinical practice and will overestimate the costs and benefits of vericiguat treatment. The PSCR acknowledged that this will overestimate costs, but claimed it will not overestimate benefits as they are derived directly from the VICTORIA clinical trial data, and therefore account for treatment adherence/ persistence in the trial. However, the ESC considered that the trial-based outcomes will only account for treatment compliance during the trial period (median duration of follow-up of 10.8 months), while the model extrapolates outcomes to 10 years. The extrapolated period of the model does not account for subsequent treatment discontinuation or treatment adherence patterns and would therefore overestimate the benefit in patients in the extrapolated period.	Unclear impact

Source: Constructed during the evaluation with reference to Section 3 of the submission and A7.1_Vericiguat_CEM_PBAC_Nov21_v3.0 spreadsheet provided with the submission

*The submission calculated a monthly discontinuation rate of 3.57% based on 38.6% of patients discontinuing vericiguat over a median follow-up duration of 10.8 months. Assuming a fixed, linear trend, the submission estimated that all patients would discontinue treatment by 28 months. The submission assumed the mid-point of 28 months would represent the average treatment duration of all patients (calculated as $0.5 \times 28 = 14$ months).

6.38 The figure below presents the model trace for vericiguat plus standard of care and standard of care alone for the subgroup of patients in NT-proBNP quartiles 1-3 (model base case).

Figure 3: Model traces for vericiguat plus standard of care and standard of care alone: NT-proBNP Q1-Q3 subgroup



Source: Constructed during the evaluation using A7.1_Vericiguat_CEM_PBAC_Nov21_v3.0 spreadsheet provided with the submission
 Abbreviations: CV, cardiovascular; Hosp (first and subseq), patient in first or subsequent hospitalisation event, or post-first or subsequent hospitalisation event health states; No hosp, patient who hasn't experienced a hospitalisation; SOC, standard of care; Ver, vericiguat

6.39 The model traces indicate that vericiguat was associated with a survival benefit, due to a reduction in cardiovascular death; with a smaller benefit associated with a reduction in hospitalisation. This was inconsistent with the results of the VICTORIA trial (ITT and NT-proBNP Q1-Q3 subgroup), which showed the difference between treatment arms was primarily driven by differences in the rates of hospitalisation for heart failure. The benefit of vericiguat treatment is maintained over the 10 year duration of the model. At the end of the 10-year time horizon, 35-40% of patients remain alive.

6.40 The ESC noted that vericiguat was associated with a survival benefit that continued over the 10-year time horizon and considered this was not adequately justified given the median duration of follow-up in the trial (10.8 months). Further, the ESC considered that, unlike other cardiovascular drugs that have modelled a prolonged survival benefit beyond the trial follow-up (e.g. the PCSK9-inhibitors), vericiguat was not associated with biologically plausible disease modification (but rather an alteration in biochemical modulators while taking the drug). The ESC considered that, given the lack of evidence to support a prolonged survival benefit, it may be more appropriate for the economic model to be primarily driven by reduced cardiovascular hospitalisations, rather than mortality benefits.

6.41 During the evaluation, the number of hospitalisations per patient, cardiovascular deaths and all-cause deaths derived from the VICTORIA trial were compared with events in the economic model over a 15 month time horizon (consistent with average follow-up for hospitalisation events and all-cause mortality in the VICTORIA trial). The ITT population was used as there were insufficient data available for the NT-proBNP Q1-Q3 subgroup from the VICTORIA trial to enable a comparison with the model base case population.

Table 11: Comparison of outcomes in the ITT population of the VICTORIA trial with modelled results based on the ITT population over 15 months of follow-up

	VICTORIA trial	Model estimates at 15 months ^a
Hospitalisations per patient (first and subsequent events)		
- vericiguat + SoC	0.484 ^b	0.289
- SoC	0.529 ^c	0.333
Hospitalisations per patient (first event)		
- vericiguat + SoC	0.274 ^b	0.214
- SoC	0.296 ^c	0.253
Hospitalisations per patient (subsequent events)		
- vericiguat + SoC	0.211 ^b	0.020
- SoC	0.233 ^c	0.028
Cardiovascular death		
- vericiguat + SoC	16.4% ^d	11.1%
- SoC	17.5% ^e	12.4%
All-cause mortality		
- vericiguat + SoC	20.3% ^f	12.1%
- SoC	21.2% ^g	13.4%

Source: Table 11-3, p109; Table 11-7, p127; Table 11-8, p128 and Table 11-10, p133 of the VICTORIA trial CSR, and A7.1_Vericiguat_CEM_PBAC_Nov21_v3.0 spreadsheet provided with the submission

Abbreviations: CV, cardiovascular; ITT, intention to treat; SoC, standard of care

^a time period based on average follow-up for hospitalisation events and all-cause mortality in the VICTORIA trial; see Tables 11-7 and 10-18 of the CSR.

^b based on 1,223 events in 2,526 patients (first and subsequent); 691/2,526 (first event); 532/2,526 (subsequent events)

^c based on 1,336 events in 2,524 patients (first and subsequent); 747/2,524 (first event); 589/2,524 (subsequent events)

^d based on 414 CV deaths in 2,526 patients

^e based on 441 CV deaths in 2,524 patients

^f based on 512 all-cause deaths in 2,526 patients

^g based on 534 all-cause deaths in 2,524 patients

6.42 The comparison indicates that the model significantly underestimates hospitalisation events, cardiovascular mortality and non-cardiovascular mortality compared with the VICTORIA trial on which estimates were based, over a similar average duration of follow-up. The model estimates that the hospitalisation events observed in the VICTORIA trial would only be reached after 36 months, compared with an average duration of follow-up for hospitalisation events in the VICTORIA trial of 15 months. This suggests that the regression analyses and parametric models used to extrapolate outcomes do not reliably predict observed outcomes over the trial period and therefore should not form the basis of further extrapolation over 10 years.

6.43 The results of the stepped economic evaluation are summarised in the table below.

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Table 12: Results of the stepped economic evaluation (NT-proBNP Q1-Q3 subgroup; discounted)

Step and component	Vericiguat + SoC	Placebo + SoC	Increment	ICER
Step 1: Time horizon 11 months, drug costs only, outcome life years (no discounting)				
Costs	\$ ¹	\$ ¹	\$ ¹	\$ ⁶
Life-years*	0.8834	0.8782	0.0052	
Step 2: Time horizon increased to 10 years (costs and outcomes discounted at 5% per year)				
Costs	\$ ²	\$ ⁵	\$ ⁵	\$ ⁴
Life-years*	5.4515	5.1626	0.2889	
Step 2a: Health state utilities included, outcomes quality adjusted life years (QALYs)				
Costs	\$ ²	\$ ⁵	\$ ⁵	\$ ⁷
QALYs	3.9137	3.6938	0.2199	
Step 3: Routine care and monitoring costs included				
Costs	\$ ³	\$ ²	\$ ⁵	\$ ⁷
QALYs	3.9137	3.6938	0.2199	
Step 4: Terminal care costs included				
Costs	\$ ⁴	\$ ³	\$ ⁵	\$ ⁷
QALYs	3.9137	3.6938	0.2199	
Step 5: Hospitalisation costs included				
Costs	\$ ⁴	\$ ³	\$ ⁵	\$ ⁴
QALYs	3.9137	3.6938	0.2199	

Source: Table 3-22, p186 of the submission

Abbreviations: ICER, incremental cost-effectiveness ratio; NT-proBNP, N-terminal-pro B-type natriuretic peptide; QALY, quality-adjusted life year; SoC, standard of care

* The submission's stepped economic evaluation was based on QALY outcomes only. During the evaluation, the submission's stepped analysis was adapted to assess the impact of health state utilities (life years were used as the outcome for the first two steps).

The redacted values correspond to the following ranges:

- ¹ \$0 to < \$5,000
- ² \$15,000 to < \$25,000
- ³ \$25,000 to < \$35,000
- ⁴ \$35,000 to < \$45,000
- ⁵ \$5,000 to < \$15,000
- ⁶ \$255,000 to < \$355,000
- ⁷ \$45,000 to < \$55,000

6.44 The extrapolation of outcomes beyond the clinical trial duration and the introduction of health state utilities had the largest impact on the stepped economic evaluation.

6.45 Table 13 presents the results of the modelled economic evaluation for the base case NT-proBNP Q1-Q3 subgroup compared to the ITT population.

Table 13: Results of the modelled economic evaluation

Component	Vericiguat + SoC	Placebo + SoC	Increment
Base case (VICTORIA NT-proBNP Q1-Q3 subgroup; discounted)			
Costs	\$ ¹	\$ ²	\$ ³
QALYs	3.9137	3.6938	0.2199
Incremental cost/QALY gained			\$¹
Overall population (VICTORIA ITT; discounted)			
Costs	\$ ¹	\$ ²	\$ ³
QALYs	3.5170	3.3538	0.1632
Incremental cost/QALY gained			\$⁴

Source: Table 3-25, p187 of the resubmission

Abbreviations: QALY, quality-adjusted life year; SoC, standard care.

The redacted values correspond to the following ranges:

- ¹ \$35,000 to < \$45,000
- ² \$25,000 to < \$35,000

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³ \$5,000 to < \$15,000

⁴ \$55,000 to < \$75,000

- 6.46 Based on the modelled economic evaluation of the base case population (NT-proBNP Q1-Q3 subgroup), treatment with vericiguat plus standard care was associated with an incremental cost per QALY gained of \$35,000 to < \$45,000. Based on the ITT population, vericiguat plus standard care was associated with an incremental cost per QALY gained of \$55,000 to < \$75,000.
- 6.47 The cost-effectiveness estimate may not be reliable given that:
- The structure of the economic model was similar to other models that the PBAC has previously considered were overly simplistic as they did not account for progressive nature of heart failure.
 - The ESC considered it was not appropriate to base the economic analysis on a subgroup of patients defined by NT-proBNP $\leq 5,314$ pg/mL, without having a similar criterion in the proposed restriction to identify these patients.
 - The transition probabilities estimated in the model (through the use of post-hoc regression analysis and parametric extrapolations) were poorly justified and do not appear to reliably predict observed outcomes during the trial period.
- 6.48 The results of key sensitivity analyses presented in the submission and conducted during the evaluation are summarised in the table below.

Table 14: Results of sensitivity analyses based on the VICTORIA NT-proBNP Q1-Q3 subgroup

Analyses	Incremental cost (\$)	Incremental QALY	ICER (\$)
Base case (VICTORIA NT-proBNP Q1-Q3 subgroup)	1	0.2199	2
Discount rate (base case 5% costs and outcomes)			
- 0% costs and outcomes	1	0.2907	2
- 3.5% costs and outcomes	1	0.2384	2
Time horizon (base case 10 years)			
- 5 years	1	0.0918	3
- 20 years	1	0.3732	2
Starting age of the patient population (base case: 66.65 years)			
- 75 years (lvabradine PSD, November 2011 PBAC)	1	0.2038	4
- 85 years	1	0.1556	4
Transition 1: Probability of hospitalisation (base: case log-normal extrapolation function)			
- Exponential extrapolation (most favourable)	1	0.2508	5
- Generalised gamma extrapolation (least favourable)	1	0.2145	4
Transition 2: Pre-hospitalisation to death (base case: generalised gamma extrapolation function)			
- Exponential extrapolation (most favourable)	1	0.2331	2
- Log-normal extrapolation (least favourable)	1	0.2186	4
Transition 5: Post-hospitalisation to death (base case: log-normal)			
- Gompertz extrapolation (most favourable)	1	0.2942	5
- Generalised gamma extrapolation (least favourable)	1	0.2135	4
Risk of hospitalisation or death (base case: no increased risk post hospitalisation extrapolation function)			
- 46% increased risk (Voors et al., 2017)	1	0.2364	2
Hospitalisation case fatality rate (base case: 5.78%)			
- decrease by 50%	1	0.2154	4
- increase by 50%	1	0.2242	2
Hospitalisation costs (base case: \$8,707)			
- decrease by 50%	1	0.2199	4
- increase by 50%	1	0.2199	2
Terminal care costs (base case: \$14,232)			
- decrease by 50%	1	0.2199	4
- remove terminal care costs	1	0.2199	4
Utility of alive (no hospitalisation) health state (base case: 0.737)			
- decrease by 20% (disutility of hospitalisation health states remains constant)	1	0.1771	3
- increase by 20% (disutility of hospitalisation health states remains constant)	1	0.2627	2

Source: Table 3-26, pp188-189 of the submission and additional calculations performed during the evaluation using A7.1_Vericiguat_CEM_PBAC_Nov21_v3.0 spreadsheet provided with the submission

Abbreviations: HF, heart failure; ITT, intention-to-treat; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; Q, quartile

The redacted values correspond to the following ranges:

1 \$5,000 to < \$15,000

2 \$35,000 to < \$45,000

3 \$55,000 to < \$75,000

4 \$45,000 to < \$55,000

5 \$25,000 to < \$35,000

6.49 The economic model was most sensitive to changes in the VICTORIA trial population (ITT versus NT-proBNP Q1-Q3 subgroup), the time horizon, and the utility of the alive (no hospitalisation health state).

Drug cost/patient

6.50 Drug costs in the economic model and financial estimates differed due to differences in adherence and treatment discontinuation estimates, as summarised in the table below. Both costing approaches were inadequately justified in the submission and were inconsistent with trial data.

Table 15: Drug cost per patient for vericiguat

	VICTORIA trial	Economic model	Financial estimates
Daily dose ^a	2.5 mg: 9.1% 5 mg: 9.0% 10 mg: 81.9%	10 mg	2.5 mg: 9.1% 5 mg: 9.0% 10 mg: 81.9%
Adherence	95.3% ^b	100%	95.3% ^b
Treatment discontinuations	38.6% including 14.2% due to deaths over mean duration of follow-up of 12.5 months	No discontinuations. Modelled cardiovascular and non-cardiovascular deaths	42.9% discontinuations including deaths at 12 months ^c
Treatment duration	Mean duration of treatment 12.34 months, over mean duration of follow-up of 12.5 months	Ongoing in surviving patients (average duration 6.67 years)	14 months fixed duration ^d
Number of scripts	-	13.04 per year ^e	Initial year: 12.43 ^f Subsequent year: 2.06 ^g
Cost per script	-	DPMQ \$	DPMQ \$
Cost per patient	-	\$ per year	\$ per patient (fixed) ^h

Source: Table 2-18, pp90-92 of the submission; 'A7.1_Vericiguat_CEM_PBAC_Nov21_v3.0' spreadsheet provided with the submission; 'A8_Vericiguat_Section 4 UCM_PBAC_Nov2021_V3.0' spreadsheet provided with the submission; Table 10-1, p58 of the VICTORIA trial clinical study report.

^a Patients in the VICTORIA trial initiated on vericiguat 2.5 mg daily with titration to a target dose of 10 mg daily based on blood pressure and symptom criteria. The mean average dose of study drug reported over the course of the study was 7.8 mg. Population split across doses (2.5mg, 5mg, and 10mg) based on the status over the entire treatment period.

^b Mean treatment compliance reported in the VICTORIA trial.

^c The proportion of patients who discontinued or died after 1 year was extrapolated based on the median follow-up duration of 10.8 months in the trial (calculated as 38.6% ÷ 10.8 x 12 = 42.9%).

^d The submission calculated a monthly discontinuation rate of 3.57% based on 38.6% of patients discontinuing vericiguat over a median follow-up duration of 10.8 months. Assuming a fixed, linear trend, the submission estimated that all patients would discontinue treatment by 28 months. The submission assumed the mid-point of 28 months would represent the average treatment duration of all patients (calculated as 0.5 x 28 = 14 months).

^e Calculated as 365.25 days ÷ 28 days script coverage

^f Calculated as 365.25 days ÷ 28 days script coverage x 95.3% adherence

^g The submission assumed that continuing patients would receive a further 2 months of treatment based on an average treatment duration of 14 months. The number of scripts per patient was estimated as 2.06 based on 2.17 scripts to cover 2 months of treatment, adjusted by 95.3% adherence.

^h Total scripts per patient calculated as 12.43 + 2.06 = 14.49. Cost per patient calculated as 14.49 x DPMQ \$ = \$

Estimated PBS usage & financial implications

6.51 The submission was considered by DUSC. The submission used an epidemiological approach to estimate the utilisation and financial impact.

Table 16: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Eligible population		

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Parameter	Value applied and source	Comment
Prevalence of HF	1.5%; based on a systematic review of the prevalence or incidence of heart failure in Australia published between 1990 and 2015 (Sahle 2016). The submission used 1.5% as the midpoint of the range of prevalence estimates (1.0-2.0%).	In November 2020, DUSC advised the prevalence estimate of 1.5% to be an underestimate of heart failure in Australia (para 6.60, dapagliflozin PSD, November 2020 PBAC meeting). DUSC considered an alternative prevalence of 2.199% reported in the SHAPE study, a retrospective analysis of heart failure patients in Australian primary care (Liew 2020).
Proportion of patients with HFrEF, LVEF <45%	59.9%; based on an unpublished retrospective analysis of acute care heart failure admissions to South Australian public hospitals between January 2012 and December 2019 (Chew et al, September 2021 South Australia Heart Failure Registry final study report). At the index admission, 59.85% of all heart failure patients had LVEF <45%.	This proportion was similar to the proportion of patients with HFrEF (LVEF ≤40%) of 57% previously considered by the PBAC in the September 2021 dapagliflozin submission (Table 15, dapagliflozin PSD, September 2021 PBAC meeting). DUSC has previously noted alternative estimates of HFrEF from an analysis of the SHAPE study of primary care records (62%) and SNAPSHOT-HF study based on acute heart failure admissions (58%) (para 6.60, dapagliflozin PSD, November 2020 PBAC meeting).
Proportion of patients with NYHA class II-IV	88%; based on a survey of the sponsor's advisory board (Attachment 9.2 of the submission). The submission used the mean estimate of proportion of patients in NYHA class II-IV with a worsening HF event in the last 6 months.	The applicability of this estimate was uncertain as the range of responses varied between 70-100%. The PBAC previously considered a 95% estimate of patients with HFrEF with LVEF ≤40% are in NYHA class II-IV, used in the September 2021 dapagliflozin submission and July 2016 sacubitril/valsartan submission (Table 15, dapagliflozin PSD, September 2021 PBAC meeting).
Proportion of patients with a worsening HF event	26.6%; based on an unpublished retrospective analysis of the South Australian Heart Failure Registry (Chew et al, September 2021). The submission used the estimated event rate for re-hospitalisation for heart failure within 12 months of the index event in all patients with heart failure.	The applicability of this estimate was uncertain as it was based on re-hospitalisations within 12 months of the index hospitalisation, which is narrower in definition than in the proposed restriction (any recent decompensation event, no timeframe specified). The estimate was also based on all HF patients in the study which may not be applicable to the target population with symptomatic HFrEF. The Chew study indicated increasing rates of re-hospitalisations based on subgroups simulating the trial inclusion criteria (51.8% in the subgroup with recent hospitalisation (≤6 months) and 76.4% in the subgroup with recent hospitalisation, LVEF <45%, elevated NT-proBNP and eGFR>15 mL/min/1.73m ² . The PBAC considered that this estimate was likely overestimated even with the narrower revised restriction in which timeframes were specified for the decompensation event (hospitalisation in the past 6 months or intravenous diuretic therapy for heart failure (without hospitalisation) in the past 3 months).

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Parameter	Value applied and source	Comment
Treated with ACEi/ARB or ARNi	90%; based on a survey of the sponsor's advisory board. The sum of mean percentages for patients with HFREF who are on an ACEi/ARB or ARNi was 90% prior to a worsening event and 89% after a worsening event.	The requested restriction requires patients to be on the maximum tolerated dose of a beta-blocker and mineralocorticoid receptor antagonist in addition to an ACEi/ARB/ARNi. The proportion of patients who are receiving standard care was uncertain as it also allows for treatment of patients who are contraindicated/intolerant to standard care therapies. DUSC considered that 90% would be an overestimate and noted that the submission indicated 58.7% of patients in the vericiguat treatment group of the VICTORIA trial were using a beta-blocker, mineralocorticoid receptor antagonist (MRA) and an ACEi/ARB/ARNi.
Proportion of patients stabilised after a worsening HF event	77.2%; based on an unpublished retrospective analysis of the South Australia Heart Failure Registry (Chew et al, September 2021 report). An NT-proBNP quartile analysis of all patients with test results at the index presentation indicated 77.17% of patients were in the first three quartiles (see Table 4.1.3, Attachment 4 of the commentary). This estimate was used as a proxy for patients who have stabilised after a worsening event.	The clinical relevance of NT-proBNP levels and stabilisation following a worsening event was uncertain. The quartile analysis is a statistical tool used to determine the range of NT-proBNP estimates that would divide the patient numbers into four quartiles. The estimate used in the submission appeared arbitrary, with the range of NT-proBNP estimates representing each quartile varying between the VICTORIA trial and Chew analyses of all patients and subgroup analyses of cohorts emulating the VICTORIA trial. Data from the Chew analyses were also limited due to the relatively small proportion of patients with NT-proBNP results (32%). DUSC considered that due to the aforementioned issues and the MBS restrictions, the value of 77.2% was likely underestimated. However, the PBAC considered that other restriction criteria would be required to target use to stabilised patients, and thus the estimate of 77.2% was unlikely to be an underestimate.
Treatment utilisation		
Uptake rate	█% in Yr 1, increasing to █% in Yr 6. The uptake rate in Year 6 was based on the mean estimate of treatment uptake (█%) if vericiguat is PBS-listed without NT-proBNP testing requirements, based on a survey of the sponsor's advisory board.	The survey responses to treatment uptake were wide-ranging, from █% to █%. In addition, uptake of vericiguat is uncertain given the lack of clarity regarding its use as an add-on to SoC including SGLT2 inhibitors. DUSC considered the uptake rates to be overestimated and stated that "clinicians are likely to prefer the well-known SGLT2 inhibitors over a novel and unfamiliar treatment". The PBAC considered vericiguat would be used after SGLT2 inhibitors in the treatment algorithm, which would comprise a very small, late-line place in therapy and thus uptake would likely be substantially lower than estimated by the submission.

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Parameter	Value applied and source	Comment
Initial year scripts	12.43 per patient; based on 13.04 scripts per year, adjusted for 95.3% adherence in the trial.	Trial-based treatment adherence may not be applicable to clinical practice. DUSC considered adherence of 95.3% was likely overestimated considering that the proportion of patients on any dose of sacubitril/valsartan (including once daily or twice daily dosing) was approximately 86-89%. ³
Proportion of surviving patients continuing treatment after 1 year	57.1%; based on the proportion who discontinued treatment in the vericiguat arm of the trial of 38.6% inclusive of deaths (14.2%), adjusted to 1 year based on median follow-up duration of 10.8 months in the trial (calculated as 38.6% ÷ 10.8 x 12 = 42.9%). The proportion of surviving patients who continued treatment was calculated as 100% - 42.9% = 57.1%.	The estimated proportion of surviving patients who continued treatment was inappropriately calculated assuming a fixed, linear trend in discontinuation rates over time. The submission did not adequately justify the use of median follow-up duration that required extrapolation given the trial reported a mean follow-up duration of 12.5 months. The incorporation of deaths in treatment discontinuations may result in double-counting as deaths are already considered in prevalence estimates. DUSC considered it likely that there would be a high number of initial discontinuations soon after initiating treatment followed by long term survivors whose treatment duration would be underestimated by the application of a linear trend.
Average treatment duration	14 months. The monthly discontinuation/death rate was estimated as 3.57% based on 38.6% treatment discontinuations/deaths in the trial over a median follow-up duration of 10.8 months. Assuming a fixed, linear trend, the submission estimated that all patients would discontinue treatment by 28 months. The submission assumed the mid-point of 28 months would represent the average treatment duration of all patients.	No data were provided in support of the assumption of a fixed discontinuation/death rate over time, which was also inappropriately derived using median duration of follow-up rather than mean duration of follow-up. The average treatment duration was based on unsupported assumptions and unlikely to reflect the duration of treatment in practice. The assumed circumstances of use were inconsistent with the economic model that was based on 100% treatment adherence and persistence.
Continuing year scripts	The submission assumed that continuing patients would receive a further 2 months of treatment based on an average treatment duration of 14 months. The number of scripts per patient was estimated as 2.06 based on 2.17 scripts to cover 2 months of treatment, adjusted by 95.3% adherence.	The estimated number of scripts was reliant on the assumed average treatment duration that was inappropriately derived (see above).

Source: Sections 4.1 to 4.2, pp 191-200 of the submission

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; HF, heart failure; HRrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; NT-proBNP, N-terminal -pro hormone brain natriuretic peptide

6.52 The submission did not request a grandfathering provision. However, the submission noted that a planned vericiguat Patient Access Program (PAP) for approximately <500 patients will be commenced after TGA approval and prior to PBS listing. The submission claimed treatment eligibility criteria for the PAP would be identical to the

³ Wachter R et al. Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study. Eur J Heart Fail. 2019 Aug;21(8):998-1007. doi: 10.1002/ejhf.1498. Epub 2019 May 27. PMID: 31134724.

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proposed PBS restriction, which would allow for these patients to transition to PBS-subsidised treatment after listing. Details of the PAP eligibility criteria were not provided in the submission. The submission claimed these patients are already included in the prevalent population estimates and the uptake rates were assumed to include patients who would switch from the PAP to PBS-subsidised treatment following PBS-listing.

6.53 The table below presents the estimated financial impact of listing vericiguat.

Table 17: Estimated number of treated patients and prescriptions

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Eligible population						
Australian population age ≥18 years	20,757,917	21,082,471	21,411,852	21,744,502	22,073,220	22,393,101
Heart failure prevalence (1.5%)	311,369	316,237	321,178	326,168	331,098	335,897
LVEF <45% (59.9%)	186,354	189,268	192,225	195,212	198,162	201,034
NYHA class II-IV (88%)	163,992	166,556	169,158	171,786	174,383	176,910
Worsening HF event (26.6%)	43,622	44,304	44,996	45,695	46,386	47,058
Treated with ACEi/ARB/ARNi (90%)	39,260	39,873	40,496	41,126	41,747	42,352
Stabilised after HF event (77.2%)	30,296	30,769	31,250	31,736	32,215	32,682
Utilisation estimates						
Treatment uptake	%	%	%	%	%	%
Initiating patients	1	1	5	5	5	2
Initial year scripts (12.43/patient)	2	4	6	9	10	10
Surviving patients who continued treatment (57.1% from prior year)	-	1	1	1	1	5
Continuing year scripts (2.06/patient)	-	1	5	5	5	2
Total scripts	2	4	7	10	10	10
Net PBS/RPBS cost	\$ ³	\$ ³	\$ ⁸	\$ ⁸	\$ ⁸	\$ ⁸

Source: Sections 4.1-4.2 (pp 191-200) of the submission

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 10,000 to < 20,000

³ \$0 to < \$10 million

⁴ 50,000 to < 60,000

⁵ 5,000 to < 10,000

⁶ 70,000 to < 80,000

⁷ 80,000 to < 90,000

⁸ \$10 million to < \$20 million

⁹ 90,000 to < 100,000

¹⁰ 100,000 to < 200,000

6.54 The estimated net cost to the PBS/RPBS was \$0 to < \$10 million in Year 1, increasing to \$10 million to < \$20 million in Year 6, a total of \$60 million to < \$70 million over 6 years.

6.55 DUSC considered the estimates presented in the submission were uncertain and that the main issues were:

- The proposed restriction was broader than the VICTORIA trial inclusion criteria and open to the interpretation of the prescriber. DUSC suggested changes be made to the restriction to define a more appropriate population.

- The financial estimates presented in the submission were uncertain with several inputs underestimated including the prevalence of heart failure and treatment duration. Other inputs such as the number of stabilised patients, treatment uptake and compliance were likely overestimated in part due to the changing landscape of heart failure treatment with the positive recommendation of SGLT2 inhibitors for this condition.
- Previously DUSC advised a prevalence of heart failure with reduced ejection fraction of 2.199% reported in the SHAPE study (Liew 2020) to be appropriate. Increasing prevalence from 1.5% up to 2% will increase the total cost in year 6 from \$18.9 million to \$23.6 million.
- Due to the uncertainty and current MBS restrictions of the N-terminal pro hormone B-type natriuretic peptide (NT-proBNP) test as a measure of stability in current clinical practice the proportion of patients stabilised after a heart failure event was likely to be underestimated.
- The treatment uptake rates were overestimated as clinicians and patients are likely to prefer the well-known SGLT2 inhibitors over a novel and unfamiliar treatment.

Quality Use of Medicines

- 6.56 The submission stated that the sponsor will promote quality use of medicines through medical education for health professionals and consumers.

Financial Management – Risk Sharing Arrangements

- 6.57 No risk sharing arrangement was proposed in the submission.

7 PBAC Outcome

- 7.1 The PBAC did not recommend vericiguat for the treatment of patients with symptomatic chronic heart failure who are stabilised after a recent decompensation event requiring hospitalisation and/or intravenous diuretic therapy and are on concomitant standard of care (SoC) therapies. The PBAC considered that vericiguat was associated with modest efficacy in a small group of high-risk patients. The PBAC advised that the proposed PBS restriction required revision to align more closely with these high-risk patients. Further, the PBAC considered the subgroup of patients included in the economic evaluation as a proxy for identifying stabilised patients was not an appropriate approach to the assessment of cost-effectiveness. The PBAC considered that the economic model should be revised to reflect the ITT population of the key trial and that the incremental cost-effectiveness ratio (ICER) was unacceptably high and uncertain at the proposed price. The PBAC considered, therefore, that a price reduction would be required to achieve a cost-effective listing

and the financial estimates would need to be revised, along with an RSA, to ensure PBS expenditure was restricted to this small group of patients.

- 7.2 The PBAC noted that a range of therapies are available for this patient group but considered there remained a clinical need for a therapy with a different mechanism of action in a specific, narrowly defined group of high-risk patients with acute decompensated heart failure who are haemodynamically stable and clinically euvolaemic.
- 7.3 The PBAC considered that the proposed place in therapy, after ACEi/ARBs/ARNis, beta-blockers, MRAs, SGLT2 inhibitors and diuretics, in patients who are stable after a recent decompensation event, was appropriate and considered this would be a late-line niche place in therapy. The PBAC considered that it was important that the restriction appropriately identify this small group of patients.
- 7.4 The PBAC noted that the proposed restriction did not align with the population identified as most likely to benefit from vericiguat in the key trial. In the VICTORIA trial, the NT-proBNP Q1-Q3 post-hoc subgroup population (NT-proBNP $\leq 5,314$ pg/mL) was used to inform the economic evaluation base case. The PBAC noted that NT-proBNP is not a validated indicator of stabilisation post-ADHF and testing is not currently funded through the MBS for the required purpose. The sponsor had argued that the NT-proBNP Q1-Q3 subgroup was a proxy for identifying 'stabilised' patients, however the PBAC also noted the ESC's advice that it would be difficult to reliably identify this population in clinical practice without measuring NT-proBNP (for example, the VICTORIA trial excluded patients who were considered clinically unstable at baseline, however 24% of patients enrolled still had a NT-proBNP $> 5,314$ pg/mL).
- 7.5 The ESC had considered that unless this issue was explored through a new integrated codependent submission, input of the ITT population into the economic model would be appropriate. On balance, the PBAC did not consider that an integrated codependent submission was clinically appropriate and that the ITT population should be considered for the clinical and cost effectiveness. Given the clinical need was in a small group of high-risk patients, the listing should restrict use to patients who match the VICTORIA trial population as much as practical, without reference to baseline NT-proBNP, and with initiation limited to cardiologists.
- 7.6 As such, the PBAC advised that the listing for vericiguat should specify:
 - vericiguat must be initiated under the supervision of a specialist cardiologist;
 - the initial restriction should be Authority Required (telephone/online), and the continuing restriction should be Authority Required (Streamlined);
 - a time frame for the recent decompensation event consistent with the VICTORIA trial, which required patients to have had a heart failure hospitalisation in the past 6 months or intravenous diuretic therapy for heart failure (without hospitalisation) in the past 3 months;

- criteria to identify stabilised patients, namely that the patient must be haemodynamically stable and clinically euvolaemic (i.e. the patient must not have: clinical signs of fluid overload; received IV treatment in the previous 24 hours; or have a systolic blood pressure less than 100 mmHg);
 - vericiguat must be an add-on therapy to optimal standard chronic heart failure treatment including a beta-blocker and an ACEi/ARBs/ARNi unless contraindicated;
 - that the patient is symptomatic with NYHA class II, III or IV, and has documented LVEF of less than 45% (as proposed in the submission); and
 - a grandfather restriction to ensure that, at initiation of therapy, patients enrolled in the patient access program met the PBS criteria around experiencing a recent decompensation event and being euvolaemic.
- 7.7 The PBAC considered that the comparator nominated by the submission, which effectively was standard of care (SoC) (including ACEi/ARBs/ARNis, beta-blockers, MRAs, and diuretics) was appropriate, noting vericiguat would be used in addition to SoC. The PBAC considered that, in clinical practice, it is likely that SGLT2 inhibitors (dapagliflozin and empagliflozin) will be used as SoC, prior to vericiguat.
- 7.8 The PBAC noted that the VICTORIA trial recruited a higher risk population than other recent trials in heart failure (including the SGLT2 inhibitor HFREF trials DAPA-HF and EMPEROR-Reduced), given it enrolled patients who were stabilised following a recent acute decompensation event. The PBAC considered the median duration of follow-up in the trial, at 10.8 months, was short for a therapy intended for chronic usage, but acknowledged this was due to the high-risk population targeted who experienced high event rates, in the context of an event-driven trial.
- 7.9 The PBAC considered that the magnitude of benefit associated with vericiguat plus SoC in the VICTORIA ITT population was modest and primarily driven by differences in the rate of hospitalisation for heart failure. The PBAC noted that the absolute risk reduction (ARR) for the primary outcome, a composite of time to cardiovascular death or heart failure hospitalisation, was 3% (event rate of 35.5% in the vericiguat arm versus 38.5% in the placebo arm) which was similar in magnitude to recent trials of other heart failure therapies (DAPA-HF and EMPA-Reduced had approximately 5% ARR), but this was in the context of a higher risk population as evidenced by the high event rate in the placebo arm. Overall, the PBAC considered that the clinical data indicated modest efficacy in high-risk patients in a late-line of therapy in the ITT population.
- 7.10 The PBAC considered that the magnitude of the incremental benefit seen in the VICTORIA Trial may overestimate the potential benefit in the proposed PBS population given:
- There were key differences between the trial population and the likely PBS population in terms of baseline NT-proBNP, age, gender, eGFR and concomitant

medicines (as outlined in Paragraph 6.8) which suggest that the likely PBS population may include patients with more severe disease, who may not achieve the same benefits associated with vericiguat observed in the VICTORIA trial. The PBAC noted that pre-specified subgroup analyses demonstrated that NT-proBNP and age were treatment effect modifiers, with worse outcomes experienced in patients with higher NT-proBNP and older age.

- The estimated treatment effects were based on a population with substantially lower use of ARNi therapies (sacubitril/valsartan) and limited exposure to SGLT2 inhibitors, which is no longer reflective of clinical guidelines. The magnitude of benefit associated with the addition of vericiguat to standard therapy including SGLT2 inhibitors is unknown.
- 7.11 The PBAC noted that while the magnitude of the vericiguat treatment effect was larger in the post-hoc Q1-3 NT-proBNP subgroup than the Q4 subgroup, there was no formal test for interaction for NT-proBNP Q1-Q3 or adjustments for multiplicity. Also, the PBAC considered that this population would be difficult to adequately identify in clinical practice, given NT-proBNP is not routinely measured in Australian clinical practice and is not reimbursed by the MBS for this indication (as outlined in Paragraph 7.4). The PBAC considered that this subgroup may be more readily identified if initiation was restricted to cardiologists, but overall did not accept this subgroup was an appropriate basis for assessing the clinical or cost effectiveness of vericiguat.
- 7.12 The PBAC considered that the claim of comparable safety was likely reasonable but noted that vericiguat was associated with a slight increase in drug-related adverse events compared with placebo (14.6% versus 11.7%, respectively). Overall, the PBAC considered that vericiguat appeared to be reasonably well tolerated.
- 7.13 The PBAC noted the issues with the economic model that had been raised by the commentary and the ESC including:
- The structure of the economic model was overly simplistic as it did not account for progressive nature of heart failure.
 - The transition probabilities estimated in the model (through the use of post-hoc regression analyses and parametric extrapolations) were poorly justified and did not appear to reliably predict observed outcomes during the trial period i.e. the model significantly underestimated hospitalisation and mortality events, and overestimated the mortality benefit associated with vericiguat.
 - The submission assumed perfect adherence and compliance to vericiguat in surviving patients over the 10-year duration of the model (an average treatment duration of 6.67 years). This will not reflect persistence in clinical practice and will overestimate the costs and benefits of vericiguat treatment.
- 7.14 The PBAC noted that the economic analysis was based on a subgroup of patients defined by NT-proBNP $\leq 5,314$ pg/mL (the NT-proBNP Q1-Q3 subgroup), and considered this was inappropriate in the absence of a corresponding criterion in the

restriction to identify these patients. While the PBAC proposed a narrower restriction identifying stable patients, this was unlikely to correspond exactly with the exclusion of the Q4 subgroup. Thus, the PBAC considered that the ITT results of the VICTORIA trial should be applied in the model, which increased the ICER from \$35,000 to < \$45,000/QALY gained to \$55,000 to < \$75,000/QALY gained (refer to Table 13).

- 7.15 The PBAC considered that an ICER of \$55,000 to < \$75,000/QALY gained was overly high in the context of the likely overestimated magnitude of mortality benefit (refer to paragraph 7.10) and the uncertain estimate of the ICER given the aforementioned issues with the model. The PBAC advised that an ICER of up to \$40,000/QALY gained (using the ITT results of the VICTORIA trial in the model) would be required for vericiguat to be considered suitably cost-effective. The PBAC noted that a price reduction would be required to achieve this ICER. In the context of this price reduction, a narrower restriction limiting use to a late-line place in therapy and financial estimates that reflect this niche positioning, the PBAC considered that the submission's model may provide an acceptable basis for decision making.
- 7.16 The PBAC considered that, overall, the financial estimates presented in the submission were overestimated and that the following parameters should be amended:
- the prevalence rate should be increased from 1.5% to 1.85%, to be the mid-point between the submission's estimate of 1.5% and the alternate estimate discussed in the DUSC advice of 2.2% which was reported in the SHAPE study, a retrospective analysis of heart failure patients in Australian primary care (Liew 2020).
 - the uptake rate, which the submission assumed to be |% in Year 1 increasing to |% in Year 6, based on a clinician survey. The PBAC considered vericiguat would be used after SGLT2 inhibitors in the treatment algorithm, and noted that the submission had not accounted for this place in therapy given the estimates only included the proportion of patients treated with an ACEi/ARB/ARNi (90%). Overall, the PBAC considered that vericiguat would have a very small, niche place in therapy with the restriction limiting initiation to cardiologists. Further, the target population will comprise patients receiving multiple other cardiovascular medicines who may be reluctant to add another therapy. The PBAC considered that a substantially lower uptake rate would be required.
 - the proportion of patients with a worsening heart failure event (26.6%) was likely overestimated given the narrower restriction outlined in Paragraph 7.6), which specifies timeframes for the decompensation event. The PBAC noted that the submission had tested this parameter in sensitivity analyses, using lower and upper limits of 10.1% and 27.0% based on the results of a review of published literature from 2000–2016 assessing the re-admission rate (including those for HF) following a cardiovascular hospitalisation in the Australian setting (Labrosciano et al., 2020). The PBAC considered the proportion would be less than 26.6% but not

as low as 10.1%, and that around one-fifth of patients (20%) would be an acceptable proportion for the purposes of financial estimates.

- adherence (assumed to be 95.3% in the submission) would likely be closer to 86% to 89% (as was reported to be observed with sacubitril/valsartan)
- 7.17 The PBAC considered that given the overall uncertainty with the economic model a risk sharing arrangement (RSA) would be required to manage the risk of use outside the narrow restriction in a less responsive patient group, given clinical judgement will be required to identify stable patients.
- 7.18 The PBAC considered the outstanding issues could be easily resolved in a simple resubmission for vericiguat using the early re-entry pathway. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation:
- Amend the restriction as outlined in Paragraph 7.6;
 - An ICER of less than \$40,000/QALY gained with the ITT results of the VICTORIA trial applied in the model;
 - Revised financial estimates as outlined in Paragraph 7.16 and to include the lower price resulting from the aforementioned changes to the economic model; and
 - Outline an RSA to manage the risk of use in a broader population.
- 7.19 The early re-entry resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early re-entry timing is not acceptable, a standard re-entry pathway is available.
- 7.20 The PBAC advised that its acceptance of the submission's model was in the context of a price reduction, a narrow restriction limiting use to a late-line niche place in therapy and financial estimates that reflect this niche place, including an RSA. Alternatively, the issues with the economic model (outlined in Paragraph 7.11) would need to be addressed in a standard re-entry resubmission.
- 7.21 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

8 Context for Decision

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

through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

While the PBAC's decision not to recommend vericiguat for the treatment of high-risk patients with symptomatic chronic heart failure (HF) is disappointing, Bayer welcomes the PBAC's consideration of the clinical unmet need for these high-risk patients and will continue to work with the PBAC to enable earliest possible access to vericiguat for these patients.