5.10 SACUBITRIL WITH VALSARTAN, tablets, sacubitril 24 mg + valsartan 26 mg, sacubitril 49 mg + valsartan 51 mg, sacubitril 97 mg + valsartan 103 mg, Entresto®, Novartis

1 Purpose of Application

1.1 The submission requested Section 85 Authority Required (STREAMLINED) listing of sacubitril with valsartan for the treatment of chronic heart failure with reduced ejection fraction.

2 Requested listing

2.1 The requested PBS listing is presented below.
Suggestions and additions are in *italics* and in ~~strikethrough~~ for deletions.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
SACUBITRIL + VALSARTAN sacubitril 24 mg + valsartan 26 mg tablet, 56 sacubitril 49 mg + valsartan 51 mg, tablet, 56 sacubitril 97 mg + valsartan 103 mg, tablet, 56"	1	5	$[redacted] $[redacted] $[redacted]	Entresto® NV

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Severity:	Chronic
Condition:	Heart failure
PBS Indication:	Chronic heart failure
Treatment phase:	Initiation
Restriction Level / Method:	☐ Restricted benefit ☐ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☒ Streamlined

Clinical criteria:	Patient *must be symptomatic with* NYHA classes II, III or IV AND Patient must have a documented left ventricular ejection fraction (LVEF) of less than or equal to 40% AND Patient must receive concomitant optimal standard chronic heart failure treatment, which must include the maximum tolerated dose of a beta-blocker, unless contraindicated or not tolerated. AND *The treatment must not be co-administered with an ace inhibitor (ACE-I) or an angiotensin II receptor blocker (ARB).*
Administrative Advice	**Continuing therapy only** For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.

2.2 The submission presented a cost-utility analysis of sacubitril/valsartan compared with enalapril, as a proxy for all angiotensin converting enzyme (ACE) inhibitors.

2.3 The PBAC considered that it would be appropriate for the restriction to require that patients already be stabilised on ACE inhibitor or ATRA therapy.

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

3 Background

3.1 The submission was made under TGA/PBAC Parallel Process. At the time of PBAC consideration, sacubitril/valsartan had been registered. The approved TGA indication was for use in adult patients for the treatment of chronic heart failure (New York Heart Association (NYHA) class II-IV) with reduced ejection fraction.

3.2 Sacubitril/valsartan is a fixed-dose combination of sacubitril, a neprilysin inhibitor, and valsartan, an off-patent angiotensin II receptor antagonist (ATRA). Sacubitril monotherapy has not demonstrated clinically meaningful reductions in blood pressure. It is given with an ATRA because sacubitril increases angiotensin II. It is not given with an ACE inhibitor because the combination increases the risk of angioedema.

3.3 The PBAC had not previously considered sacubitril/valsartan.

4 Clinical place for the proposed therapy

4.1 Chronic heart failure is characterised by a structural abnormality or cardiac dysfunction that impairs the ability of the heart ventricle to fill with or eject blood. Reduced ejection fraction, or systolic, heart failure refers to a weakened ability of the heart to contract in systole. Symptoms are classified into four levels (I to IV) using the NYHA grading system. NYHA class I refers to no limitations, while class IV refers to symptoms at rest.

4.2 Treatment for NYHA classes II to IV typically consists of ACE inhibitors, beta-blockers and, if there is fluid overload, a diuretic. ATRAs are recommended as an alternative to ACE inhibitors in patients who cannot tolerate ACE inhibitors.

4.3 The submission proposed that sacubitril/valsartan be used in patients with chronic heart failure (NYHA class II-IV) with an ejection fraction of 40% or less. The drug was proposed as a first-line treatment replacing the maximally tolerated dose of an ACE inhibitor or an ATRA.

4.4 The submission stated that listing of sacubitril/valsartan would not impact the use of other co-administered therapies, such as cardio-selective beta-blockers, diuretics, and later-line therapies such as spironolactone, digoxin and ivabradine.

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

5 Comparator

5.1 Enalapril, as a proxy for all ACE inhibitors, was nominated as the main comparator. ACE inhibitors, at appropriate doses, are appropriate comparators for a first-line place in therapy.

5.2 The submission appropriately nominated ATRAs as a secondary comparator. However, due to a lack of evidence, the submission did not conduct a formal clinical comparison of the two treatments, and no economic comparisons were made.

5.3 A comparison with valsartan alone would have assisted in determining the value of adding sacubitril to valsartan alone.

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 discussed the clinical need in this condition, when patient prognosis is often poor despite the availability of a number of therapies. The clinician also responded to concerns in the Commentary and ESC Advice about the doses used in the key trial, discussing the doses likely to

be used for this product and current clinical practice for existing therapies, and addressed other matters in response to the Committee's questions. The clinician provided useful information on dose-response data from the trial. The hearing was useful

Consumer comments

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

Clinical trials

6.3 The submission was based on one head-to-head trial comparing sacubitril/valsartan with enalapril (8,442 patients randomised).

6.4 Details of the trial presented in the submission are provided in the table below.

Table 1: Trial presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial(s)		
PARADIGM-HF	A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic heart failure and reduced ejection fraction (NCT01035255)	31 October 2014
	McMurray J, Packer M, Desai A, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure.	NEJM 2014; 371 (11): 993-1004
	Claggett B, Packer M, McMurray J, et al. Estimating the Long-Term Treatment Benefits of Sacubitril–Valsartan.	NEJM 2015; 373 (23): 289-2290

Source: Table 14, pp49-50 of the submission

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

Table 2: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
PARADIGM-HF	8,442 [a]	R, MC, DB Median follow-up: 27 months	Low to unclear	CHF, NYHA class II-IV with reduced ejection fraction [b]	Composite of CV death or first HF hospitalisation.	CV mortality, CV and HF hospitalisation, change in mean NYHA class.

Source: *Compiled during the evaluation*

CHF = chronic heart failure; CV = cardiovascular DB = double blind; HF = heart failure; MC = multi-centre; NYHA = New York Heart Association; r = randomised

[a] Number of patients randomised. 10,513 patients entered the first run-in period.

[b] Reduced ejection fraction was in initially defined as left ventricular ejection fraction of ≤ 40%, but was changed to ≤ 35% in a protocol amendment.

6.6 PARADIGM-HF was a multicentre, controlled trial with two main phases:

- A single-blind run-in phase. Patients received enalapril 10 mg twice daily for two weeks. If this was tolerated, patients received sacubitril/valsartan 49/51 mg for one to two weeks, then 97/103 mg for two to four weeks.
- Patients who tolerated both run-in periods entered the double-blind randomised treatment phase.

6.7 Overall, approximately 80% of patients who enrolled in the first run-in period were randomised into the double-blind treatment period (the full analysis set). Patients who were randomised had less severe disease than those enrolled, as demonstrated by a lower proportion of NYHA class III or IV failure (24.8% and 35.7 %, respectively). The run-in period limited the applicability of the trial to the requested population. Further, the trial outcomes might not reflect the comparative efficacy in patients treated with lower doses of sacubitril/valsartan (since patients in the study could be treated with the maximum recommended dose).

6.8 The trial was conducted in 47 countries. There were no trial centres in Australia. The diverse range of health care systems would influence hospitalisation rates, all-cause mortality and cardiovascular mortality. The latter is influenced by a range of factors including access to other medicines, health services and other technologies such as implantable cardioverter-defibrillators. These factors might influence the comparative efficacy of sacubitril/valsartan versus enalapril. For example, a modelled survival analysis of the PARADIGM-HF data by Claggett (2015) showed that, compared with enalapril, sacubitril/valsartan had less impact on overall survival in patients in North America and Western Europe than in patients in Latin America, Central Europe and Asia-Pacific. Outcomes from the trial might be difficult to translate to Australian practice.

6.9 To enrol in the trial, patients were required to have been on a stable dose of ACE inhibitor or ATRA (equivalent to at least 10 mg per day of enalapril) for at least four weeks. This might have introduced survivor bias. Over half of the randomised patients were diagnosed more than two years prior to entering the trial. Under the proposed restriction, treatment-naive patients would be able to initiate on sacubitril/valsartan.

6.10 The trial compared:

- Half the maximum dose of enalapril recommended in some guidelines (20 mg daily in the trial); with
- The maximum recommended dose of valsartan, in combination with sacubitril. (The dose of valsartan was equivalent to 320 mg daily. Due to differences in bioavailability, 103 mg valsartan in sacubitril/valsartan is equivalent to 160 mg valsartan in the single ingredient table. This was administered twice daily).

6.11 The dose of enalapril was based on the pivotal trial of enalapril in heart failure, which was conducted in the late 1980s (SOLVD-Treatment). However, clinical practice has changed since this time. Table 3 compares the maximum and mean doses in PARADIGM-HF with the doses recommended in the Australian Product Information and various guidelines. Some of the benefit of sacubitril/valsartan might have been due to the relatively higher dose of valsartan, rather than the novel sacubitril component.

Table 3: Dosing of enalapril versus valsartan in PARADIGM-HF and Australian practice

	Daily doses in trial, mg		Recommended daily doses	
	Max dose	Mean dose	Australian Product Information	Guidelines [c]
Equivalent valsartan dose in sacubitril/valsartan [a]	320 mg	300 mg [b]	160-320 mg	Up to 320 mg
Enalapril	20 mg	18.9 mg [b]	10-20 mg	Up to 40 mg

Source: Table 12-4, p304 of the Clinical Study Report; and compiled during evaluation
max = maximum
[a] Valsartan has a higher bioavailability in the sacubitril/valsartan fixed-dose combination than in the single ingredient table. The dose expressed here is the equivalent dose of valsartan in single ingredient tablet. The equivalent doses are: sacubitril/valsartan 24/26 mg = 40 mg valsartan, 49/51 mg = 80 mg valsartan; 97/103 mg = 160 mg valsartan. This was administered twice daily.
[b] Mean dose excluding interruptions, safety set, last available record during randomised period in patients still taking the study medication.
[c] Therapeutic Guidelines (Cardiovascular Expert Group, 2012) and the National Prescribing Service (2011), American College of Cardiology Foundation/ American Heart Association (Yancy et al, 2013).

6.12 The difference in potency between the doses used in the trial was further supported by the HEAVEN trial (Willenheimer 2002) in which valsartan 160 mg daily was shown to be non-inferior to enalapril 20 mg in terms of exercise capacity in heart failure. That is, the dose of enalapril used in the PARADIGM-HF trial was non-inferior to half the dose of valsartan used in PARADIGM-HF for the outcome of change in six-minute walk test at 12-weeks.

Comparative effectiveness

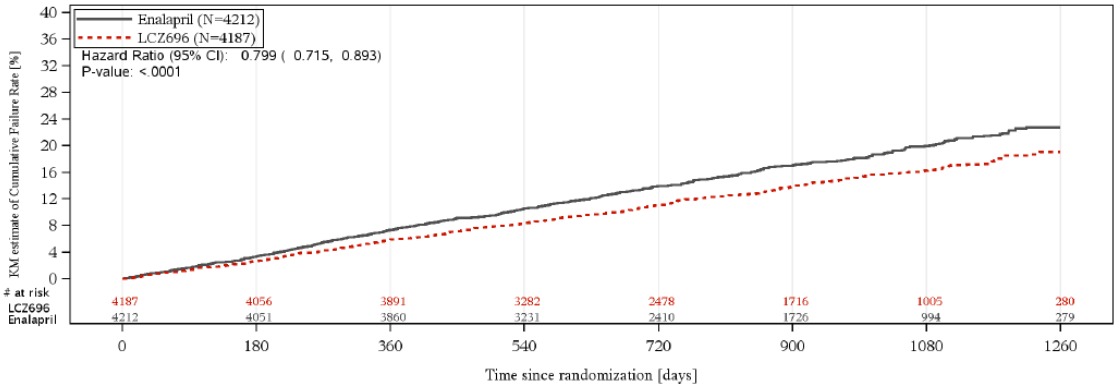
6.13 The primary outcome of PARADIGM-HF was a composite of time to cardiovascular death or first heart failure hospitalisation post-randomisation. The trial was also powered to demonstrate superiority in cardiovascular mortality. Table 4 summarises the results of the primary outcome and its components from PARADIGM-HF and Figure 1 presents the Kaplan-Meier curves for cardiovascular death.

Table 4: Results of primary outcomes from PARADIGM-HF, full analysis set

	Sacubitril/ valsartan N = 4,187	Enalapril N = 4,212	Hazard ratio %, (95% CI)[a]
Median duration of follow-up, months	*27.2*	*27.0*	
Primary composite endpoint, n (%) time to either CV death **or** first HF hospitalisation	914 (21.8%)	1,117 (26.5%)	**0.80 (0.73, 0.87)**
CV death, n (%)	558 (13.3%)	693 (16.5%)	**0.80 (0.71, 0.89)**
First HF hospitalisation, n (%)	537 (12.8%)	658 (15.6%)	**0.79 (0.71, 0.89)**

Source: Table 29, p92 of the submission
CI = confidence interval; CV = cardiovascular; HF = heart failure; **Bold** = statistically significant
[a] The analysis was performed using a Cox-regression model with treatment and region as fixed factors.

Figure 1: Kaplan-Meier plot for cardiovascular death by treatment (PARADIGM-HF), full analysis set



Source: Figure 13, p 93 of the submission.
CI = confidence interval; LCZ696 = sacubitril/valsartan

6.14 Sacubitril/valsartan resulted in a reduction in cardiovascular death compared with enalapril (hazard ratio: 0.80; 95% confidence interval (CI): 0.71 to 0.89).

Comparative harms

6.15 Table 5 outlines the safety outcomes from the run-in phase of PARADIGM-HF.

Table 5: Run-in phase: Summary of adverse events that led to discontinuation (> 1% of patients)

PARADIGM-HF	Sacubitril/valsartan n = 9,419 [a] n with event/N (%)	Enalapril n = 10,513 [a] n with event/N (%)
Discontinued due to adverse event	551 (5.9%)	591 (5.6%)
Hypotension	164 (1.7%)	146 (1.4%)
Hyperkalaemia	125 (1.3%)	174 (1.7%)
Renal dysfunction	174 (1.9%)	181 (1.7%)
Other	132 (1.4%)	102 (1.0%)
Withdrawn consent	100 (1.1%)	171 (1.6%)

Source: Table 43, p124 of the submission
[a] Based on patients who entered the relevant run-in phase. Patients could only enter the sacubitril/valsartan run-in phase if they tolerated the enalapril run-in phase. Therefore more patients entered the enalapril run-in phase than the sacubitril/valsartan.

6.16 A similar percentage of patients discontinued treatment due to an adverse event in the run-in phases for enalapril and sacubitril/valsartan. However, only patients who tolerated enalapril entered the sacubitril/valsartan run-in phase, and thus adverse events with sacubitril/valsartan might be under-reported. On the other hand, the run-in phase was longer for sacubitril/valsartan than for enalapril.

6.17 Table 6 outlines the safety outcomes from the double-blind, randomised phase of PARADIGM-HF.

Table 6: Double-blind phase: Adverse events (summary and those with an incidence > 2% in any group)

PARADIGM-HF	Sacubitril/valsartan n with event/N (%)	enalapril n with event/N (%)	RD (95% CI)
N, safety set	4,203	4,229	
Any AE	3,419 (81.3%)	3,503 (82.8%)	*-1.5% (-3.1%, 0.2%)*
Any serious AE	1,937 (46.1%)	2,142 (50.7%)	***-4.6% (-6.7%, -2.4%)***
AE leading to discontinuation	450 (10.7%)	516 (12.2%)	*-1.5% (-2.9%, 0.1%)*
Any drug-related AE (at least one)	910 (21.6)	976 (23.1)	-1.4% (-3.2%, 0.4%)
Hypotension	430 (10.2)	293 (6.9)	**3.3% (2.1%, 4.5%)**
Hyperkalemia	193 (4.6)	237 (5.6)	**-1.0% (-2.0%, -0.1%)**
Renal impairment	117 (2.8)	179 (4.2)	**-1.4% (-2.2%, -0.7%)**
Cough	64 (1.5)	161 (3.8)	**-2.3% (-3.0%, -1.6%)**

Source: Tables 44- 45, pp125-126 of the submission
AE = adverse event; CI = confidence interval; RD = risk difference

6.18 There were more serious adverse events in the enalapril arm than the sacubitril/valsartan arm. However, the run-in phase was longer for sacubitril/valsartan than for enalapril, so patients had to tolerate sacubitril/valsartan for longer prior to entering the double-blind phase.

6.19 The comparative safety of sacubitril/valsartan versus enalapril in a population who have not completed a run-in phase is unknown.

Benefits/harms

6.20 A summary of the comparative benefits and harms for sacubitril/valsartan versus enalapril is presented in the table below.

Table 7: Summary of comparative benefits and harms for sacubitril/valsartan versus enalapril: (randomised phase)

PARADIGM-HF	Sacubit/ val	Enalapril	HR (95% CI)	Event rate/100 patients [a]		RD (95% CI)
				Sacubit/ val	Enalapril	
Benefits						
Primary composite endpoint	914/4,187	1,117/4,212	**0.80 (0.73,0.87)**	21.8	26.5	NR
CV death	558/4,187	693/4,212	**0.80 (0.71, 0.89)**	13.3	16.5	NR
First HF hospitalisation	537/4,187	658/4,212	**0.79 (0.71, 0.89)**	12.8	15.6	NR
Harms						
	Sacubit/ val	**Enalapril**	**RR (95% CI)**	**Event rate/100 patients [a]**		**RD (95% CI)**
				Sacubit/ val	**Enalapril**	
Adverse event, randomised phase						
Any serious AE	1,937/4,203	2,142/4,229	**0.91 (0.87, 0.95)**	46.1	50.7	**-4.6% (-6.7%, -2.4%)**
AE leading to discontinuation	450/4,203	516/4,229	**0.88 (0.78, 0.99)**	10.7	12.2	-1.5% (-2.9%, 0.1%)
Hypotension	430/4,203	293/4,229	**1.48 (1.28, 1.70)**	10.2	6.9	**3.3% (2.1%, 4.5%)**
Hyperkalaemia	193/4,203	237/4,229	**0.82 (0.68, 0.99)**	4.6	5.6	-1.0% (-2.0%, -0.1%)
Angioedema	19/4,203	10/4,229	1.91 (0.89, 4.11)	0.45%	0.24%	0.2% (0.0%, 0.5%)

Source: Table 29, p92; Table 31 p96; Table 44, p125 of the submission; Table 12-12, p319 of the Clinical Study Report;
AE = adverse event; CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; NR = not reported; RD = risk difference; RR = relative risk; Sacubit/ val = sacubitril/valsartan; **Bold** = statistically significant
[a] Median follow-up for sacubitril/valsartan 27.2 months, for enalapril 27.0 months

6.21 On the basis of direct evidence presented by the submission, for every 100 patients with chronic cardiac failure and systolic dysfunction , and who are able to tolerate the target drugs, treated with sacubitril/valsartan, in comparison with enalapril,10mg BD, over a median follow-up of 27.1 months:

- Approximately 3 fewer patients would experience cardiovascular death.
- Approximately 5 fewer patients would experience a serious adverse event.
- Approximately 3 more patients would experience hypotension.

Clinical claim

6.22 The submission described sacubitril/valsartan as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over enalapril.

6.23 The claim of superior efficacy was supported by the data presented, however it was difficult to accurately quantify the magnitude of the benefit of sacubitril/valsartan compared with ACE inhibitors, or compared with valsartan alone, in the proposed Australian population because:

- The dose of enalapril was half the maximum dose recommended in many guidelines, while the dose of valsartan in sacubitril/valsartan was the maximum dose.
- The trial used a run-in design in which only patients who tolerated the trial's target doses for at least two weeks were randomised. This reduced the applicability of the results.

- Hospitalisation, cardiovascular mortality and all-cause mortality outcomes might not reflect the results that would be seen in Australian practice.

6.24 The claim of non-inferior safety might not be adequately supported due to the lack of reliable comparative safety data, in the context of a new class of drug. In particular, the following safety concerns were noted by the Commentary and ESC:

- Safety data from the run-in period could not be compared across the two arms because only patients who tolerated enalapril entered the sacubitril/valsartan run-in period.
- The randomised period only included patients who could tolerate at least two weeks of both drugs at the trial's target doses, and therefore is not applicable to the proposed PBS population.
- No long-term safety data were available.
- The observed increase in hypotension with sacubitril/valsartan was more likely to translate into dizziness and falls in the treated older, more comorbid PBS population.
- There were a number of quality use of medicines issues that may impact on safety (see Quality Use of Medicines, below).

6.25 The PBAC considered that the claim of superior comparative effectiveness was reasonable, but noted that it was difficult to quantify the magnitude of this benefit accurately.

6.26 The PBAC considered that the claim of non-inferior comparative safety was reasonable, only in a selected population that tolerated ACE inhibitor therapy. This selected population may not be generalisable to the proposed PBS population who are not necessarily pre-treated with an ACE inhibitor, and may be older and frailer.

Economic analysis

6.27 The submission presented a cost-utility analysis based on the direct randomised trial, PARADIGM-HF. Sacubitril/valsartan was compared with enalapril, as a proxy for all ACE inhibitors.

Table 8: Summary of model structure and rationale

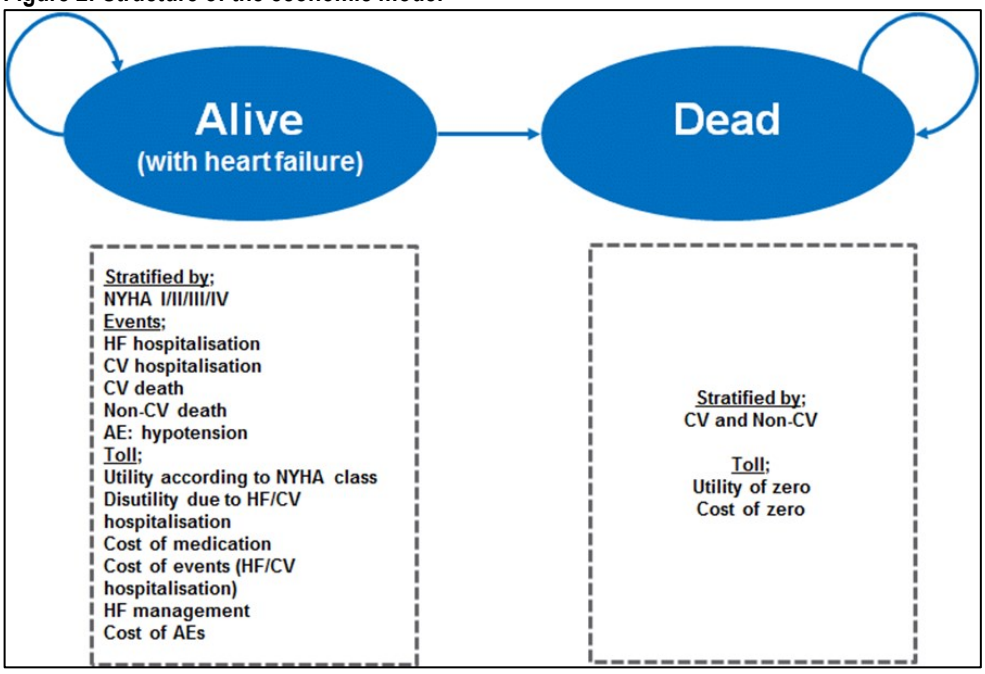
Component	Summary
Time horizon	10 years in the base case versus median follow-up of 27.1 months in the trial
Outcomes	Life years gained and QALYs
Methods used to generate results	Markov model, 1000-patient cohort expected value analysis.
Health states	Alive (with HF) and dead. In the alive (with HF) health state, patients could experience: non-CV death; CV death; HF hospitalisation; CV hospitalisation; or a hypotensive adverse event. Patients were distributed across the NYHA classes (I to IV) for the purposes of attributing a corresponding utility score.
Cycle length	One month
Transition probabilities	For CV death based on extrapolation of KM curves using exponential distribution, with no adjustment for the older age of the cohort. For other cause death, based on ABS life-tables and AIHW GRIM data, adjusted for the older age of the cohort.

Source: Compiled during the evaluation

ABS = Australian Bureau of Statistics; AIHW = Australian Institute of Health and Welfare; CV = cardiovascular; GRIM = General Record of Incidence of Mortality; HF = heart failure; KM = Kaplan-Meier; NYHA = New York Heart Association; QALY = quality-adjusted life year

6.28 The model structure, as shown in Figure 2, comprised two health states: alive (with heart failure) and dead. There were five events that a patient could experience in the alive (with heart failure) health state each cycle: non-cardiovascular death; cardiovascular death; hospitalisation due to heart failure; hospitalisation due to cardiovascular causes; or a hypotensive adverse event. Patients could have more than one of these events in each cycle.

Figure 2: Structure of the economic model



Source: Figure 40, p239 of the submission

AE = adverse events; CV = cardiovascular; HF = heart failure; NYHA = New York Heart Association

6.29 Patients in the alive (with heart failure) health state were distributed across the classes of NYHA heart failure (I to IV), and this was only used for the purpose of

attributing a corresponding utility score. Transitions between disease severities were not explicitly modelled. Therefore, in the model, rates of events were independent of previous events or disease severity.

6.30 The two-state model structure did not accurately reflect disease progression through hospitalisation and rehospitalisation and through different NYHA functional classes of heart failure. This does not reflect the progressive nature of heart failure. The ESC considered that the failure of the model to better reflect disease progression meant that it was unlikely to be reliable for estimating incremental cost-effectiveness.

6.31 The assumption that NYHA class distribution will remain the same beyond 24 months in the trial was not reasonable or supported.

6.32 Cardiovascular mortality, which was a key driver of the model, was based on trial data until median follow-up, then extrapolated using the best-fitting parametric curve. In the model, the underlying risk of cardiovascular mortality was assumed to be the same as that of the patients in PARADIGM-HF, and was assumed to be independent of age, NYHA class and other co-variates. Thus, the underlying cardiovascular mortality was based on a cohort of patients with an average age of 64 years, who had completed a run-in period (the run-in period filtered out the patients with the most severe disease). Further, over half of the randomised patients were diagnosed more than two years prior to entering the trial, and so might reflect a relatively stable population. As such, the model did not reflect the different baseline risk in the PBS population compared with the trial population. This was not appropriate as patients aged 75 years and over have higher cardiovascular mortality than those under 75 years (in the enalapril arm of the trial, 17% of patients aged 75 years and over died due to cardiovascular causes, compared with 12.5% of those under 75 years). The model did not adequately adjust for a different baseline cardiovascular risk in the Australian population compared with the trial population.

6.33 In the model, half of the patients were still alive at ten years, despite a starting age of 75 years. The external validity of the model was not tested.

6.34 Costs in the model were incurred independently of NYHA risk. Costs were significantly underestimated

6.35 Table 9 presents the key drivers of the economic model.

Table 9: Key drivers of the model

Description	Method/Value	Impact
Risk of CV death	KM data from trial until median follow-up, then extrapolation using the exponential function, with no adjustment for the older age of the cohort	High, favours sacubitril/valsartan
Time horizon	10 years; from 27.1 month median follow-up in the trial	High, favours sacubitril/valsartan
Continuing treatment effect	KM data from trial until median follow-up, then extrapolation using the exponential function	High, favours sacubitril/valsartan

Source: Compiled during the evaluation
CV = cardiovascular; KM = Kaplan-Meier

6.36 The results of the stepped economic evaluation are presented in the table below.

Table 10: Results of the stepped economic evaluation

Step and component	Sacubitril/valsartan	Enalapril	Increment
Step 1: Trial-based costs and outcomes – 2.25 years (drug costs only)			
Costs	$ [redacted]	$ [redacted]	$ [redacted]
CV deaths	[redacted]	[redacted]	[redacted]
Incremental cost/CV death avoided			**$** [redacted]
Step 2: Modelled evaluation (utilities included)			
Costs	$ [redacted]	$ [redacted]	$ [redacted]
QALYs	[redacted]	[redacted]	[redacted]
Incremental cost/extra QALY gained			**$** [redacted]
Step 3: Modelled evaluation (time horizon increased to 10 years)			
Costs	$ [redacted]	$ [redacted]	$ [redacted]
QALYs	[redacted]	[redacted]	[redacted]
Incremental cost/extra QALY gained			**$** [redacted]
Step 4: Modelled evaluation (all costs included)			
Costs	$ [redacted]	$ [redacted]	$ [redacted]
QALYs	[redacted]	[redacted]	[redacted]
Incremental cost/extra QALY gained			**$** [redacted]

Source: Table 101, p261 of the submission

CV = cardiovascular; QALY = quality-adjusted life year

6.37 The submission estimated an incremental cost-effectiveness ratio (ICER) of $105,000 - $200,000 per cardiovascular death avoided and $15,000 - $45,000 per quality-adjusted life year gained. The results of the economic model were unreliable due to a number of assumptions made in the submission.

6.38 Table 11 provides the results of the key univariate sensitivity analyses presented by the submission and conducted during the evaluation.

Table 11: Results of key sensitivity analyses

Univariate analyses	Δ costs	Δ QALY	ICER
Base case	$		$
Extrapolation CV mortality – (base case exponential)			
Weibull	$		$
log-normal	$		$
95% CI for CV death:			
0.71	$		$
0.89	$		$
Convergence CV mortality (base case none)			
28 months (i.e. no benefit of sacubitril/valsartan beyond the trial)	$		$
5 years	$		$
Treatment effect discontinues at 28 months	$		$
Non-CV mortality			
Epidemiological based survival option	$		$
Hospitalisations			
CV/HF Hospitalisation: excluding Latin America and Asia Pacific	$		$
Utilities (base case, utilities were assigned by NYHA class)			
All patients in the alive (with HF) health state have a utility = 0.78	$		$

Source: Table 104, pp266-267 of the submission

CI = confidence interval; CV = cardiovascular; HF = heart failure; ICER = incremental cost-effectiveness ratio; NYHA = New York Heart Association; QALY = quality-adjusted life year

6.39 The results of the sensitivity analyses showed that the ICER was most sensitive to cardiovascular mortality and the assumption of continuing treatment effect. However, the major uncertainties could not be reliably tested, such as the effect of a higher dose of enalapril in Australian practice, the effects of differences in cardiovascular mortality between the trial population and the potentially older Australian population, and the impact of hospitalisations and re-hospitalisations and disease progression.

6.40 While the age at baseline in the model was assumed to be 75 years, age had little influence on the ICER because, in the model, age only impacted non-cardiovascular mortality. The model did not account for the impact of age on disease severity (i.e. NYHA class) or the underlying risk of cardiovascular hospitalisation or cardiovascular death.

Drug cost/patient/year: $ per year, on-going.

6.41 The estimated cost is $ per patient per year, based on the distribution of use of each of the strengths in the clinical trial (89% on the highest strength, 9% on the mid strength, 3% on the lowest strength), and an adherence rate of 75% (per the financial estimates). This compares with a cost of $ per year for enalapril. However, the trial doses were based on patients who completed the run-in period and thus might overestimate doses in Australian practice.

Estimated PBS usage & financial implications

6.42 This submission was considered by DUSC. An epidemiological approach was used to estimate the extent of use of sacubitril/valsartan and the financial implications to the PBS/RPBS.

Table 12: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Eligible patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Number treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scripts [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS	-	-	-	-	-
Estimated total net cost					
Net cost to PBS/RPBS/MBS	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**

Source: Table 110, p278; Table 112, p281; Table 116, p284; Table 118, p287 of the submission
[a] Assuming 9.8 scripts (13.04 * 75% compliance) per year as estimated by the submission.

The redacted table above shows that at year 5, the estimated number of patients was 100,000 – 200,000 and the net cost to PBS would be more than $100 million.

6.43 The number of eligible patients was estimated based on the overall prevalence of heart failure in Australia, then the following patient groups were deducted: patients with an ejection fraction of more than 40%; NYHA class I heart failure; and the proportion of patients not currently receiving an ACE inhibitor or ATRA.

6.44 The submission estimated that 3.25 million scripts would be dispensed in the first five years of listing and the cost to the PBS/RPBS would be $[redacted] million over the first five years.

6.45 DUSC considered the number of eligible patients presented in the submission to be underestimated, as:

- The proportion of heart failure patients with left ventricular ejection fraction of 40% or less (50%) was not derived from primary sources. An alternative primary source identified by the Commentary identified a higher proportion (64%);
- The proportion of patients with NYHA class I heart failure (11%) was from a survey of heart failure patients that did not distinguish by extent of systolic dysfunction; the proportion might be lower in patients with an ejection fraction of 40% or less.
- The number of patients with NYHA stage II-IV systolic heart failure who receive ACE inhibitors or ATRAs was determined from a 10% sample. The methodology used to define coadministration is unclear. Reliance on concomitant ivabradine and heart-failure-specific beta blockers to define heart failure patients would underestimate the proportion of people supplied ACE inhibitors or ATRAs for heart failure, as ivabradine and beta blockers are later line treatments.

6.46 DUSC considered the number of treated patients presented in the submission to be overestimated, as the uptake of sacubitril/valsartan was likely overestimated. DUSC considered that substitution from ACE inhibitors may be lower than predicted by the

submission given the long established place of ACE inhibitors for first line treatment of heart failure.

6.47 DUSC considered the cost to the PBS presented in the submission may have been overestimated, as the average dose was based on the trial population who had completed the run-in period, which is not likely to reflect clinical practice.

6.48 DUSC noted that there was potential for use outside of the requested restriction in patients with preserved ejection fraction, in patients with NYHA class I heart failure, and in patients not on concomitant beta-blocker.

Quality Use of Medicines

6.49 Sacubitril is not available as an individual component and cannot be titrated individually or combined with other ATRAs.

6.50 There were a number of quality use of medicines issues that might impact negatively on the safety of sacubitril/valsartan:

- risk of accidental co-prescribing with ATRAs or ACE inhibitors.
- risk of confusion about valsartan doses due to the increase in bioavailability when it is combined with sacubitril.
- risk of adverse drug reactions from statins as co-prescribing sacubitril with statins, which is likely to occur in most patients, increases exposure to statins.

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

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of sacubitril with valsartan on the basis of uncertain cost-effectiveness in the context of high predicted financial impact.

7.2 The PBAC considered that there was a clinical need for new therapies for the treatment of chronic heart failure.

7.3 The PBAC noted that the proposed restriction would allow ACE inhibitor treatment-naïve patients to initiate on sacubitril/valsartan. The PBAC considered that it would be more appropriate for the restriction to require patients to have been stabilised on either an ACE inhibitor or ATRA therapy before treatment with sacubitril/valsartan.

7.4 The PBAC accepted enalapril, as a proxy for all ACE inhibitors, as an appropriate main comparator. The PBAC also agreed with the submission's nomination of ATRAs as a secondary comparator.

7.5 The PBAC considered that the clinical data were reasonably reliable. Regarding the issue about the dose of enalapril used in PARADIGM-HF, the PBAC noted there is a lack of data to support a dose response for ACE inhibitors, and for this reason, the actual doses used to establish the clinical benefit may be less important than usual. The PBAC noted that there is no evidence for a dose response in sacubitril/valsartan, and suggested that it might be appropriate for this to be reflected in the pricing of sacubitril/valsartan should it be listed on the PBS.

7.6 The PBAC noted that the side-effect profiles of sacubitril/valsartan and its comparators were different, but that there was no indication of worse safety for either treatment. The PBAC noted the concerns in the Commentary about the wash-in period, and that the clinical trials included just patients who could tolerate treatment, but considered this might be addressed by requiring stabilisation on alternative therapy first

7.7 The PBAC considered that the clinical claim of superior comparative effectiveness compared to enalapril was reasonable, but that size of the benefit was uncertain due to the issues with study design and early stopping of PARADIGM-HF.

7.8 The PBAC considered that the claim of non-inferior comparative safety to enalapril was reasonable, only in a selected population that tolerated ACE inhibitor therapy. This selected population may not be generalizable to the proposed PBS population who are not necessarily pre-treated with an ACE inhibitor, and may be older and frailer.

7.9 The PBAC agreed with the ESC's view that the failure of the submission's model to reflect the progression of patients through heart failure meant that the ICER generated was not reliable and therefore cost-effectiveness of sacubitril/valsartan was unknown. In particular, the PBAC were concerned that the model assumed that the underlying risk of cardiovascular mortality was the same as that of the patients in PARADIGM-HF and that this risk was independent of age, NYHA class and other co-variates.

7.10 The PBAC considered that the financial impact of listing sacubitril/valsartan was high and uncertain. The PBAC noted the advice from DUSC that the number of eligible patients may have been underestimated, but that the number of treated patients may have been overestimated. The PBAC also noted that there was potential for use outside of the requested restriction in patients with preserved ejection fraction, in patients with NYHA class I heart failure, and in patients not on concomitant beta-blocker. The PBAC considered that the high predicted financial impact of listing was of particular concern in the context of the magnitude of clinical benefit and the cost-effectiveness of treatment being unknown.

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

Outcome:
Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

Novartis will continue to work collaboratively with the PBAC and the Federal Government to ensure that Australians with systolic heart failure receive access to Entresto® (sacubitril/valsartan) through the Pharmaceutical Benefits Scheme (PBS) at the earliest possible opportunity