7.06 SACUBITRIL with VALSARTAN
sacubitril 24 mg/ valsartan 26 mg,
sacubitril 49 mg/ valsartan 51 mg,
sacubitril 97 mg/ valsartan 103 mg,
Entresto®,
Novartis Pharmaceuticals Australia

Summary of issues: previous major submission versus current minor re-submission.

	March 2016 Major submission (1st time PBAC consideration)	March 2016 PBAC Public Summary Document	July 2016 Minor re-submission
Requested listing	For the treatment of chronic heart failure; clinical criteria: Patient must be symptomatic with NYHA classes II, III or IV AND Patient must have a documented 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-I or an ARB.	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. 7.10 … 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 requested listing was revised to include the requirement that patients must have previous or current use of an ACE-I or ATRA at recommended doses, unless contraindicated or not tolerated. The potential for leakage in use in patients with preserved ejection fraction, NYHA class I heart failure and in patients not on concomitant beta-blocker remained unchanged.
Requested price and financial impact	Weighted DPMQ = $[redacted] (Sacubitril/valsartan 24 mg/26 mg = $[redacted], 49 mg/51 mg = $[redacted], 97 mg/103 mg = $[redacted]) Estimated drug cost/ patient/ year, on-going = $[redacted] Estimated net cost to the PBS/RPBS over the first five years of listing = $[redacted] million	7.5 … 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. 7.10 The PBAC considered that the financial impact of listing sacubitril/valsartan was high and uncertain… 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.	The requested DPMQ was revised to a flat-price of $[redacted] for all strengths of the FDC. Estimated drug cost/ patient/ year, on-going = $[redacted] Estimated net cost to the PBS/RPBS over the first five years of listing = $[redacted] million The estimated drug cost/ patient/ year, on-going, of the nominated comparator, enalapril, is $[redacted].

	March 2016 Major submission (1st time PBAC consideration)	March 2016 PBAC Public Summary Document	July 2016 Minor re-submission
Assumptions in budget impact model	The submission estimated that the proportion of patients with: -systolic heart failure = 50%, - NYHA class I = 11%, and market uptake rates to be: [redacted]%, [redacted]%, [redacted]%, [redacted]%, [redacted]% over the first five years of listing.	March 2016 DUSC Advice DUSC considered that the proportion of -systolic heart failure patients was underestimated, -patients with NYHA class 1 might be lower, and that the market uptake rate was likely overestimated.	The minor re-submission: -increased the proportion of patients with systolic heart failure to 64% -reduced the proportion of patients with NYHA class I to 5%, and revised the market uptake rates to: [redacted]%, [redacted]%, [redacted]%, [redacted]%, [redacted]% over the first five years of listing. The submission also included an additional step to "reduce pool of eligible patients and reflect denovo or newly diagnosed HF patients. These patients are not likely to qualify for treatment according due to the requirement of previous/current treatment with ACEI or ARB at recommended doses" (p35 of submission). The overall impact in the changed assumptions reduced the total eligible patient numbers estimated over the first five years of listing from [redacted] to [redacted]. The reduction of [redacted] patients estimated eligible over the first five years contributed more to the reduced overall financial impact (from $[redacted] million to $[redacted] million) than the price reduction from $[redacted]/day to $[redacted]/day.
Clinical evidence/ claim	The submission presented one head-to-head trial, PARADIGM-HF: RCTcomparing sacubitril/valsartan with enalapril (N = 8,442). The submission described sacubitril/valsartan as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over enalapril.	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.	No new clinical evidence was presented in the minor re-submission. The clinical claim remains unchanged from the March 2016 submission. The magnitude of clinical benefit of sacubitril/valsartan compared to enalapril remains uncertain. Although an additional clinical criterion (previous or current use of an ACE-I or ATRA at recommended doses unless contraindicated/ not tolerated) has been included in the requested listing, it does not limit eligibility to patients currently stabilised on an AEC-I or ATRA.

<table>
<tr><th></th><th>March 2016 Major submission (1st time PBAC consideration)</th><th>March 2016 PBAC Public Summary Document</th><th>July 2016 Minor re-submission</th></tr>
<tr><td>Economic analysis</td><td>The submission presented a cost-utility analysis, with a two-state Markov model, where patients could be alive (with heart failure) or dead.</td><td>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 covariates.</td><td>The structure of the model remained unchanged.

Although the minor re-submission requested a lower DPMQ, the fundamental issues with regards to the model structure remained unchanged.</td></tr>
<tr><td></td><td colspan="3">Key drivers of the economic model</td></tr>
<tr><td></td><td>Variable</td><td colspan="2">March 2016 Major submission</td><td>July 2016 Minor re-submission</td></tr>
<tr><td></td><td>Risk of CV death</td><td colspan="2">KM data from trial until median follow-up, then extrapolation using the exponential function, with no adjustment for the older age of the cohort</td><td rowspan="3">The key variables modified in the minor re-submission were:
- reduced cost of sacubitril/valsartan, and
- equal utilisation weightings for the three sacubitril/valsartan doses, and for enalapril.

The key drivers of the model remained unchanged, and all highly favoured sacubitril/valsartan.</td></tr>
<tr><td></td><td>Time horizon</td><td colspan="2">10 years; from 27.1 month median follow-up in the trial</td></tr>
<tr><td></td><td>Continuing treatment effect</td><td colspan="2">KM data from trial until median follow-up, then extrapolation using the exponential function</td></tr>
</table>

Abbreviations: ACE-I= ACE inhibitor; ATRA= angiotensin II receptor antagonist; FDC= fixed dose combination; HF= heart failure; LVEF= left ventricular ejection fraction; NYHA = New York Heart Association; RCT= randomised controlled trial

1 Purpose of Application

1.1 The minor submission requested a Section 85 Authority Required (STREAMLINED) listing of sacubitril/valsartan for the treatment of patients with chronic heart failure and a reduced left ventricular ejection fraction.

2 Requested listing

2.1 The minor submission sought the following new listing:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
SACUBITRIL/VALSARTAN				
Tablets 50 mg (sacubitril 24 mg/ valsartan 26 mg)	56	5	$[redacted]	Entresto® Novartis
Tablets 100 mg (sacubitril 49 mg/ valsartan 51 mg)	56	5	$[redacted]	
Tablets 200 mg (sacubitril 97 mg/ valsartan 103 mg)	56	5	$[redacted]	

Category / Program	GENERAL – General Schedule (s85)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Condition:	Heart Failure
PBS Indication:	Chronic Heart failure
Treatment phase:	Initial and maintenance treatment
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 class II-IV AND • Patient must have a documented left ventricular ejection fraction (LVEF) of less than or equal to 40% AND • Patient must be on optimal standard chronic heart failure treatment, which includes o previous or current use of ACE inhibitor (ACE-I) or angiotensin II receptor antagonist (ATRA) at recommended doses, unless contraindicated or not tolerated. o maximum tolerated dose of a beta-blocker unless contraindicated or not tolerated AND • Treatment should not be co-administered with an ACE-I or ATRA.
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 minor re-submission revised the requested listing for sacubitril/valsartan by limiting eligibility to patients with prior exposure to an angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor antagonist (ATRA). This was consistent with the previous PBAC advice from the March 2016 meeting 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 (7.3, PBAC Public Summary Document March 2016).

2.3 When the PBAC considered the March 2016 submission, the PBAC noted that the financial impact of listing sacubitril/valsartan was high and uncertain. The PBAC also noted that there was potential for use outside of the requested restriction in patients with preserved ejection fraction, in patients with New York Heart Association (NYHA) class I heart failure, and in patients not receiving a 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 (7.10, PBAC Public Summary Document March 2016). The PBAC noted that the additional wording in the PBS restriction effectively removed the possibility to initiate treatment with sacubitril/valsartan but did not limit eligibility to patients who have been stabilised (for a period of time, such as ≥4 weeks in the trial PARADIGM-HF inclusion criteria) on either an ACE inhibitor or ATRA therapy. Patients who have received 'previous' treatment with either of these medications, but not necessarily stabilised, are still eligible for treatment.

2.4 The proposed restriction may reduce the budget impact of a PBS listing. However, the potential for leakage remained with regard to the use of sacubitril/valsartan in patients with NYHA class I heart failure or in those who are not receiving a concomitant beta-blocker.

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

3 Background

3.1 Sacubitril/valsartan was registered with the TGA in January 2016 for the treatment of adult patients with chronic heart failure (NYHA Class II-IV) and a reduced ejection fraction.

3.2 A major submission for sacubitril/valsartan was considered by the PBAC at the March 2016 meeting. The submission was rejected by the PBAC on the basis of uncertain cost-effectiveness in the context of high predicted financial impact (7.1, PBAC Public Summary Document March 2016).

3.3 Table 1 summarises outstanding matters of concern with the March 2016 submission and how the minor re-submission has addressed them.

Table 1: Outstanding matters of concern to the PBAC

Matters of concern	How the minor re-submission addressed it
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.	The requested restriction of sacubitril/valsartan was revised accordingly, ie limiting the possibility of initiation on sacubitril/valsartan. Eligibility is restricted to patients with previous or current use of ACE inhibitor or ATRA at recommended doses, unless contraindicated or not tolerated. However, the revised wording does not limit eligibility to patients who have been stabilised (for a period of time) on either an ACE inhibitor or ATRA therapy. Patients who have received 'previous' treatment with either of these medications, but not necessarily stabilised, are still eligible for treatment.
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.	The clinical evidence comparing sacubitril/valsartan with enalapril was unchanged from the previous submission (Trial PARADIGM-HF). The minor re-submission stated that it has adjusted the proposed PBS price to address uncertainties in the results of the economic model.
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 generalisable to the proposed PBS population who are not necessarily pre-treated with an ACE inhibitor, and may be older and frailer.	An eligibility criterion was added to the requested PBS listing for sacubitril/valsartan: previous or current use of ACE inhibitor or ATRA at recommended doses, unless contraindicated or not tolerated. However, the proposed restriction did not specifically limit eligibility to patients who have been stabilised on ACE inhibitors or ATRAs at recommended doses.
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 stages of 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.	The re-submission did not update the structure of the economic model. The submission adjusted the proposed PBS list price to address uncertainties in the incremental cost-effectiveness ratio (ICER) generated by the model. Therefore the uncertainties associated with the modelled economic evaluation identified previously remain.
7.10 The PBAC considered that the financial impact of listing sacubitril/valsartan was high and uncertain……. 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.	The size of the requested PBS population was reduced by limiting the use of sacubitril/valsartan to patients with previous exposure to ACE inhibitor or ATRA. However, the concerns on the usage outside of the requested restrictions in patients with preserved ejection fraction, in patients with NYHA class I heart failure and in patients not on concomitant beta-blocker remain unchanged.

ACE = angiotensin converting enzyme; ATRA = angiotensin II receptor antagonist; NYHA = New York Heart Association
Source: Sacubitril with valsartan Minor Overview

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

4 Clinical place for the proposed therapy

4.1 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 treatment was proposed for use as first-line therapy and would replace the maximally tolerated dose of an ACE inhibitor or an ATRA. When the PBAC considered the previous sacubitril/valsartan submission at the March 2016 meeting, the Committee considered that there was a clinical need for new therapies for the treatment of chronic heart failure (7.2, PBAC Public Summary Document March 2016).

4.2 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.

5 Comparator

5.1 Enalapril, as a proxy for all ACE inhibitors, was nominated as the main comparator. This is unchanged from the previous major submission and was accepted by the PBAC at the March 2016 meeting (7.4, PBAC Public Summary Document March 2016).

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item as it was a minor submission.

Consumer comments

6.2 The PBAC noted and welcomed the input from one individual via the Consumer Comments facility on the PBS website. The individual expressed concern regarding the cost of sacubitril/valsartan when purchased privately.

Clinical trials

6.3 No new clinical trials were presented in the minor re-submission. The PBAC previously considered that the clinical data from PARADIGM-HF were reasonably reliable, although the magnitude of the benefit remained uncertain (6.25 and 7.5, PBAC Public Summary Document March 2016).

Comparative effectiveness

6.4 The trial results remain unchanged from the previous major submission considered in March 2016.

Comparative harms

6.5 The trial results remain unchanged from the previous major submission considered in March 2016.

Clinical claim

6.6 The clinical claim remains unchanged from the original submission. At the March 2016 meeting, the PBAC considered that the clinical claim of superior comparative effectiveness compared to enalapril was reasonable, but the size of the benefit was uncertain due to the issues with study design and early stopping of the PARADIGM-HF trial. The PBAC also considered that the claim of non-inferior comparative safety to enalapril was reasonable, but 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 (7.6 and 7.7, PBAC Public Summary Document March 2016). The minor submission attempted to address the PBAC's concern by including a criterion in the proposed restriction that patients must have previous or current use of an ACE-I or ATRA at recommended doses, unless contraindicated or not tolerated.

6.7 The PBAC's views on the comparative effectiveness and comparative safety of sacubitril/valsartan versus enalapril remained unchanged.

Economic analysis

6.8 In the previous major submission considered by PBAC in March 2016, the submission presented a cost-effectiveness analysis comparing sacubitril/valsartan with enalapril. The PBAC considered that the submission's model failed to reflect the progression of patients though heart failure, and the incremental cost effectiveness ratio (ICER) generated was not reliable and therefore the 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 covariates (7.9, March 2016 PBAC Meeting, Item 5.10).

6.9 The minor re-submission does not alter the economic model structure from the submission considered in March 2016 but, as noted above under 'Background', seeks to re-specify the best estimate of the base case ICER by:

- Introducing a flat-pricing structure in line with the PBAC Public Summary Document March 2016 (7.5) and based on a selected price/day. The submission proposed a price/day of $[redacted], and stated that this represented an overall [redacted]% price reduction from the previous major submission ($[redacted]/day). The price change was introduced in order to address uncertainties in the ICER estimated by the model; and
- Including weightings for the respective dose levels in the model. The submission states that this was done to reflect real world utilisation across the three dosing levels for sacubitril/valsartan and the comparator (33.3/33.3/33.3). This had no impact on the expected cost of sacubitril/valsartan due to the flat pricing structure. The minor re-submission stated that the application of equal weighting

to the comparator arm serves to reduce the cost of the comparator, which is a conservative assumption.

6.10 Results of the economic model are provided below.

Table 2: Results of the economic evaluation

	Sacubitril/ valsartan	Enalapril	Incremental	ICER ($/LY)	ICER ($/QALY)
Minor re-submission					
Cost	$	$	$	$	$
LY			$		
QALY			$		
Original submission					
Cost	$	$	$	$	$
LY			$		
QALY			$		

LY = life year; QALY = quality-adjusted life year; ICER = incremental cost effectiveness ratio
Source: Table 8, p33 of the re-submission

6.11 Table 3 presents the key drivers of the economic model:

Table 3: Key drivers of the economic 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

CV = cardiovascular; KM = Kaplan-Meier

6.12 The PBAC previously noted that the population selected for PARADIGM-HF may not be generalizable to the proposed PBS population who may be older and more frail (7.8, PBAC Public Summary Document March 2016). The PBAC considered that the model did not reflect the baseline mortality of heart failure in the PBS population. The submission stated that the average age of patients in the proposed PBS population is 75 years; whereas, the mean age of patients in PARADIGM-HF was 63.8 years. Additionally, more than two thirds of patients (70.3%) in the trial were NYHA class II, with approximately a quarter (24.1%) of all patients being NYHA class III. NYHA class IV patients made up a negligible proportion of patients randomised to treatment (n=60/8442; 0.17%).

Drug cost/patient/year: $ / year, ongoing

6.13 The estimated cost of $ /patient / year is based on an adherence rate of 75% (per the financial estimates). This compares with a cost of around $ / patient / year for enalapril.

Estimated PBS usage & financial implications

6.14 The financial estimates in the minor submission have been updated to incorporate changes in the requested listing of sacubitril/valsartan, proposed flat-pricing structure, and DUSC concerns:

- The revised PBS restrictions will require patients to demonstrate previous or current use of ACE-I or ATRA at a recommended dose (unless contraindicated or not tolerated). The re-submission stated that patients with no previous or current ACE-I and ATRA exposure are analogous to newly diagnosed patients with HF. The proportion of patients with newly diagnosed HF (2.1 per 1,000 of the population), were subtracted from the prevalent HF population.
- The proportion of heart failure patients with reduced ejection fraction has increased from 50% (from Dhingra 2014; Go 2014; McMurray 2012; Yancy 2013; Roger 2013) to 64% (based on Maggioni et al, 2010), consistent with DUSC advice (5.10.DUSC ADV.3)
- The proportion of heart failure that is NYHA Class I has decreased from 11% (based on Sosnowska-Pasiarska 2013), to 5%. The proportion of patients with NYHA class I heart failure (11%) was from a survey of heart failure patients that did not distinguish the extent of systolic dysfunction; the DUSC considered that the proportion might be lower in patients with an ejection fraction of 40% or less (5.10.DUSC ADV.3). While the sponsor did not provide a rationale for the estimate of 5%, it is consistent with the proportion of the population with NYHA class I in PARADIGM-HF.
- The uptake of sacubitril/valsartan in the first 5 years of the PBS listing was reduced, based on DUSC advice that the original estimates may have been high (5.10.DUSC ADV.3). The estimated uptake rates have decreased in years 1-5, respectively, from [redacted]%, [redacted]%, [redacted]%, [redacted]%, [redacted]% to [redacted]%, [redacted]%, [redacted]%, [redacted]% and [redacted]%.
- The dispensed price for sacubitril/valsartan reflected a flat pricing structure, based on PBAC advice (7.5, PBAC Public Summary Document March 2016).
- The re-submission also introduced equal weighting across the strengths of enalapril (as a proxy for all ACE inhibitors). The re-submission stated that this was done to reflect the flat pricing approach. This was likely to be a conservative approach and may actually underestimate the cost-offsets associated with reduced ACE-I use.

6.15 The DUSC advice (March 2016) indicated 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 receiving a concomitant beta-blocker (5.10.DUSC ADV.3). The minor re-submission did not address these concerns.

6.16 The minor re-submission estimated a net cost to the PBS of more than $100 million in Year 5 of listing, with a total net cost to the PBS of more than $100 million over the first 5 years of listing. In Year 5, the number of patients per year is expected to be 10,000 – 50,000.

Table 4: Estimated use and financial implications

	2016	2017	2018	2019	2020
	Year 1	Year 2	Year 3	Year 4	Year 5
No. of patients per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of packs per year[1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total annual cost of sacubitril/valsartan (less co-payments)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Less reduced cost of ACE-I/ARBs	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to the PBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Table 14 and Table 5, of the re-submission

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

7. PBAC Outcome

7.1 The PBAC deferred its decision on whether sacubitril/valsartan should be listed on the Pharmaceutical Benefits Schedule (PBS) for the treatment of patients with chronic heart failure and a reduced left ventricular ejection fraction. The PBAC noted the [redacted]% price reduction of sacubitril/valsartan in the submission compared to the requested price in March 2016, but considered that this price reduction was not sufficient to account for the uncertainties surrounding cost effectiveness. The PBAC considered that a further price reduction, probably in the order of [redacted]%, would be required, with an appropriate reduction in the yearly financial cap. The PBAC considered that it would be appropriate to reduce the price of sacubitril/valsartan to the price of enalapril beyond the cap. Specifically, the PBAC recalled the previous sensitivity analyses and sought to be reassured that, at the revised price, cost effectiveness was likely to remain acceptable using model inputs more likely to reflect the PBS population.

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 recalled that it previously accepted enalapril, as a proxy for all ACE-I, as an appropriate comparator.

7.4 The PBAC recalled that it previously 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. The PBAC considered that the claim of non-inferior comparative safety to enalapril was reasonable.

7.5 The PBAC noted that the submission's model structure was unchanged from the March 2016 major submission. The PBAC recalled that it was previously concerned that the model did not accurately reflect the disease progression of patients with heart failure and the baseline heart failure mortality was not reflective of that for the likely PBS population.

7.6 The PBAC noted that the base case ICER of $15,000 - $45,000 per QALY gained in

the minor submission was lower than that in the March 2016 submission ($15,000 - $45,000). The PBAC considered that a lower ICER is required given the economic uncertainties identified.

7.7 The PBAC noted the financial impact of listing sacubitril/valsartan was high with a total net cost to the PBS of more than $100 million over the first 5 years of listing, and as such there would be a significant opportunity cost to the Commonwealth. 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.

7.8 The PBAC 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 financial risks identified should be managed through a risk-share agreement.

7.9 The PBAC considered that the submission's revised estimates of utilisation, which were based on DUSC advice (March 2016), were reasonable.

Outcome:
Deferred

ADDENDUM

At its special meeting in August 2016, the PBAC recommended the listing of sacubitril with valsartan for the treatment of patients with chronic heart failure and a reduced left ventricular ejection fraction on the basis of acceptable cost effectiveness compared to enalapril. The PBAC noted the reduced price proposed, the revised PBS expenditure estimates and considered the proposed two-tier capping levels to be a reasonable basis for the Risk Sharing Arrangement.

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 continues to work collaboratively with the PBAC and the Federal Government so that Australians with systolic heart failure are provided access to Entresto® (sacubitril/valsartan) through the Pharmaceutical Benefits Scheme (PBS) at the earliest opportunity.