

**5.03 ASUNAPREVIR
100mg, Capsule;
Sunvepra[®]; Bristol-Myers Squibb**

1 Purpose of Application

1.1 The submission requested a Section 85 Authority Required (STREAMLINED) listing for both daclatasvir (DCV) and asunaprevir (ASV) (used in combination) for the treatment of chronic Hepatitis C Virus (HCV) infection.

2 Requested listing

2.1 The requested listing for asunaprevir was:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
ASUNAPREVIR Capsule 100mg, 56	3	1	\$ [REDACTED]	Sunvepra Bristol-Myers Squibb

Treatment phase:	
Condition	Chronic genotype 1b hepatitis C infection
Restriction	Section 85 Authority required (STREAMLINED) Chronic hepatitis C infection
Treatment criteria	Evidence of chronic genotype 1b hepatitis C infection (repeatedly anti-HCV positive, HCV RNA positive and genotype 1b positive) must be documented in the patient's medical records.
Clinical criteria	Patient must have compensated liver disease, The treatment must be limited to a maximum duration of 24 weeks, The treatment must cease if the results of an HCV RNA quantitative assay at Week 8 show that the plasma HCV RNA is greater than 1000IU/mL, The treatment must be given with daclatasvir
Population criteria	Patient must be 18 years or older

2.2 The proposed listing for daclatasvir when administered in combination with asunaprevir was:

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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
DACLATASVIR Tablet 60mg, 28	3	1	\$ [REDACTED]	Daklinza Bristol-Myers Squibb

Treatment phase:	
Condition	Chronic hepatitis C infection
Restriction	Section 85 Authority required (STREAMLINED) Chronic hepatitis C infection
Treatment criteria	Evidence of chronic hepatitis C infection (repeatedly anti-HCV positive and HCV RNA positive) must be documented in the patient's medical records.
Clinical criteria	Patient must have compensated liver disease, The treatment must be limited to a maximum duration of 24 weeks, The treatment must cease if the results of an HCV RNA quantitative assay at Week 8 show that the plasma HCV RNA is greater than 1000IU/mL, The treatment must be given with asunaprevir (genotype 1b only) or sofosbuvir
Population criteria	Patient must be 18 years or older

- 2.3 The submission sought a Section 85 Authority Required (STREAMLINED) listing for both daclatasvir and asunaprevir. The current listings for the protease inhibitors are under the Section 100 Highly Specialised Drug Program.
- 2.4 There was no mention in the proposed restriction of concomitant administration with peginterferon and/or ribavirin. The draft PI for both daclatasvir and asunaprevir includes a recommended regimen of DCV+ASV+PR in patients with genotype 1 or 4 Hepatitis C Virus (HCV).
- 2.5 The requested listing did not preclude re-treating patients who had previously failed treatment with a DAA based treatment regimen. The evidence presented in the submission was for patients who had failed previous treatment with PR and not patients who have previously failed treatment with protease inhibitors or other DAAs.
- 2.6 The PBAC recalled the discussion at the Stakeholder meeting (New oral antivirals for the Treatment of Hepatitis C, February 2014) about the setting patients should be treated in. The PBAC considered that it was appropriate that the new all oral treatment regimens be listed in the General Schedule, to facilitated the longer term objectives for access to treatment, increase treatment rates and outcomes with a view to treat all patients with chronic Hepatitis C (CHC) over time.
- 2.7 Listing was sought on a cost effectiveness basis for DCV+ASV 24 weeks compared to a mixture of no treatment and active treatment.

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

3 Background

- 3.1 **TGA status at time of PBAC consideration:** The submission occurred under the TGA/PBAC Parallel Process. The clinical evaluation report for both daclatasvir and asunaprevir were provided on 30 January 2015. The TGA delegate's overview was provided on 3rd March 2015, and the drugs would be considered at the ACPM meeting to be held on 15th May 2015.
- 3.2 Asunaprevir (in combination with daclatasvir) had not previously been considered by the PBAC. Daclatasvir (in combination with sofosbuvir) was considered at the same meeting by the PBAC as a separate item.

4 Clinical place for the proposed therapy

- 4.1 The proposed treatment regimen for DCV+ASV is an all oral, interferon-free and ribavirin free option for HCV genotype 1b patients irrespective of their previous treatment history. Daclatasvir is an oral DAA and a pan-genotypic inhibitor of NS5A. Asunaprevir is also an oral DAA, an inhibitor of the HCV NS3/4A serine protease complex. The NS3/4A complex is responsible for processing the HCV polyprotein to yield mature viral proteins required for replication. The recommended dose regimen for both treatment-naïve and treatment-experienced patients with genotype 1b HCV infection was daclatasvir 60mg once daily in combination with asunaprevir 100mg twice daily for 24 weeks.
- 4.2 The proposed dose regimen was consistent with the draft PIs for each drug. It was also consistent with the dose regimens used in the clinical studies (Study 7026 and Study 7028) presented in Section B of the submission in support of the listing and in the economic evaluation.

5 Comparator

- 5.1 The submission nominated a protease inhibitor plus PR as the main comparator for DCV+ASV in HCV genotype 1b patients. The comparator may be appropriate for those patients who are currently seeking active treatments. However, the PBAC considered that the appropriate comparator was no treatment in view of the broader context of 'warehoused' infected individuals whose treatment preference would be interferon-free therapies (Paragraph 7.5, 5.17 Sofosbuvir, PSD – July 2014 PBAC meeting). Therefore 'no treatment' was presented as a comparator in the Commentary.
- 5.2 The Pre-Sub-Committee Response (PSCR, p 2) accepted that the "product" most likely to be replaced is currently "no treatment" due to the warehousing of patients. The ESC noted that in the context of the growing preference for IFN-free therapy, the most relevant was comparator was no treatment.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The sponsor reiterated key points from the submission and the pre-PBAC response. The PBAC considered that the hearing was not informative as it did not add substantively to the evidence presented in the submission.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (172), health care professionals (16) and organisations (18) via the Consumer Comments facility on the PBS website. The PBAC noted the correspondence from the Gastroenterological Society of Australia (GESA) on use of DAAs in the treatment of patients with liver cirrhosis and severe portal hypertension, decompensated liver disease, or patients post liver transplant. The large number of comments highlighted the benefit of the availability of a curative treatment that should be made available for all infected individuals and the improved quality of life as well as the side effects associated with the current treatments that would be avoided. The PBAC noted the patient preference for treatments with shorter durations, such as 12 weeks compared to 24 weeks.
- 6.3 Representatives of the PBAC met with Hepatitis Australia, Hepatitis NSW, the Australian Injecting and the Illicit Drug User's League prior to the PBAC meeting, and reported the following key points to the PBAC in relation to the agenda items for the treatment of Hepatitis C:
- The high burden of disease associated with HCV infection was noted, and the urgent need for new treatments acknowledged. The significant adverse reactions associated with interferon-based therapies effectively eliminate these regimens as an option for some patients.
 - Concern about not having any treatment (the so-called “warehousing” practice adopted by clinicians), lack of access to transient elastography (including FibroScan[®]) and the lack of adequate follow-up for patients that are “warehoused” (i.e. where the patient is monitored but treatment is delayed). A complex referral system does not work for many groups of Hepatitis C patients – for example, it was quoted in the meeting that in the ACT only 28 patients have had access to treatment in the previous 12 months.
 - Community expectation with regard to the new drugs for Hepatitis C is high, and there is a high level of anticipation with patients keenly aware that these drugs are available in markets outside Australia. It was noted that these expectations were in place for a significant time before the sponsors chose to make reimbursement submissions to the PBAC.
 - Co-ordinated treatment of HCV, particularly moving towards the control (and potentially elimination) of the virus, would require health-system-wide approaches that are outside the remit of the PBAC.
 - As the PBAC can recommend the circumstances under which PBS subsidy may be granted, elements such as whether to limit prescribing to specialists would be considered in potentially widening access. The PBAC particularly noted the advice of

consumer groups that a PBS listing that limited access based on disease severity would not be supported. A listing that allowed broad access was favoured.

- It was also noted that representatives felt that these drugs should be assessed for their capacity for providing a cure within a 12 week period, not as longer term treatment strategies.
- 6.4 The PBAC noted and welcomed this input.

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

Clinical studies

- 6.5 The submission was based on one open-label single-arm study (Study 7026) and one study that had both a randomised, double-blind, placebo-controlled component assessing safety outcomes and an open-label non-comparative component (Study 7028).
- 6.6 In Study 7028, the subgroup of treatment-naïve patients were randomly assigned to receive either DCV+ASV for 24 weeks or placebo for 12 weeks followed by 24 weeks of DCV+ASV, with blinding of treatment assignment until Week 12; the remaining patients (treatment-experienced or intolerant/ineligible to peginterferon) entered directly into the open-label non-comparative component of the study. For the assessment of comparative effectiveness, Study 7028 was essentially a single-arm study. Although comparative safety data were reported in the clinical study report (CSR), these data were not reported in the submission.
- 6.7 Study 7026 was an open-label single arm study in Japanese patients with HCV genotype 1b infection. The study included 222 patients: 87 non-responders (null or partial responders) to prior therapy with PR, and 135 patients who were either intolerant to, or ineligible for, peginterferon therapy. All patients were assigned to receive DCV+ASV for 24 weeks.
- 6.8 Details of the studies presented in the submission are provided in the table below.

Studies and associated reports presented in the submission

Study ID	Protocol title/ Publication title	Publication citation
DCV+ASV		
Study 7026	Final clinical study report for Study AI447026: A phase 3 Japanese study of BMS-790052 Plus BMS-650032 combination therapy in chronic hepatitis C genotype 1b Infected subjects who are non-response to interferon plus ribavirin and interferon-based therapy ineligible naive/intolerant Kumada, H. <i>et al.</i> , Daclatasvir plus asunaprevir for chronic HCV genotype 1b infection:	August 2013 <i>Hepatology</i> 2014; 59 (6): 2083-2091.
Study 7028	Final Clinical Study Report for Study AI447028: A phase 3 study with asunaprevir and daclatasvir (DUAL) for null or partial responders to peg-interferon alfa and ribavirin (P/R), intolerant or ineligible to P/R subjects and treatment-naive subjects with chronic hepatitis C genotype 1b infection	February 2014

Source: Table 23, p71 of the submission

6.9 The key features of the non-comparative studies are summarised below.

Key features of the included evidence

Study	N	Design/ duration	Risk of bias	Patient population	Outcome	Use in modelled evaluation
Non-comparative studies						
Study 7026	222	Single arm, OL 24 weeks after last dose	Medium*	GT 1b IFN-ineligible/intolerant and treatment-experienced**	SVR	Used [#]
Study 7028	747	Single arm of R, OL 24 weeks after last dose	Medium [^]	GT 1b treatment-naïve, IFN-ineligible/intolerant and treatment-experienced**	SVR	Used

DCV+ASV=daclatasvir and asunaprevir; OL=open label; R=randomised; GT = genotype; SVR = sustained virologic response

*Given the relevant comparator is no treatment, the risk of bias with an objective outcome, such as SVR, is low. However, there may be a high risk of bias with the subjective safety outcomes due to the open label design.

** Treatment-experienced patients are those who have failed treatment with PR.

[^] Although comparative safety data are available from the CSR of Study 7028 (the submission does not present any), the relevance to the proposed treatment regimen is low, given that the patients only received placebo for 12 weeks.

[#] Data from Study 7026 are only used in sensitivity analyses performed during the evaluation, as treatment-naïve patients (the base case modelled population) were not included in this study.

Source: compiled during the evaluation

Comparative effectiveness

6.10 The SVR rates seen in studies 7026 and 7028 are presented below.

Sustained virologic response rate following treatment with DCV+ASV for 24 weeks in Studies 7026 and 7028

Population	SVR12 (TND) ^a		SVR24 (TND) ^a	
	n/N	% (95%CI)	n/N	% (95%CI)
Treatment-naive				
Study 7028	180/203	88.7% (83.5%, 92.7%)	-	-
IFN ineligible/intolerant				
Study 7026	119/135	88.1% (81.5%, 93.1%)	118/135	87.4% (80.6%, 92.5%)
Study 7028	185/235	78.7% (72.9%, 83.8%)	-	-
Null or partial responders				
Study 7026	70/87	80.5% (70.6%, 88.2%)	70/87	80.5% (70.6%, 88.2%)
Study 7028	166/205	81.0% (74.9%, 86.1%)	-	-
Total population				
Study 7026	189/222	85.1% (79.8%, 89.5%)	188/222	84.7% (79.3%, 89.2%)
Study 7028	531/643	82.6% (79.4%, 85.4%)	-	-

CI = confidence interval; SVR = sustained virologic response; TD = target detected; TND = target not detected; IFN = interferon.

^a SVR defined as undetectable HCV RNA

Source: Table 39, p113 and Table 40, p115 of the submission.

- 6.11 SVR12 rates with 24 weeks of DCV+ASV treatment varied from 80% to 89% across the patient subgroups. The evidence suggested that the effectiveness of this combination therapy was similar in both cirrhotic and non-cirrhotic patients.
- 6.12 The submission presented a “qualitative indirect comparison” of DCV+ASV and telaprevir with peginterferon and ribavirin (TVR+PR). The submission did not present any statistical comparison of these regimens. The SVR rates presented for TVR+PR in the submission were biased if the results were reported for genotype 1 patients, as they included HCV genotype1a patients. In the table below for TVR+PR, data from the ADVANCE was presented for genotype 1b patients while data from Sitole et al (2013) included both genotype 1a and 1b treatment-experienced patients. Genotype 1a patients have lower SVR rates than genotype 1b patients, so the comparison between genotype 1b patients receiving DCV+ASV and a mixed genotype 1 population receiving TVR+PR would have favoured DCV+ASV. Despite this, a large absolute difference in SVR24 was apparent in prior non-responders, favouring DCV+ASV over TVR+PR, in an unadjusted indirect comparison performed during the evaluation.
- 6.13 Unadjusted indirect comparisons of DCV+ASV with both TVR+PR and daclatasvir with sofosbuvir (DCV+SOF) for HCV genotype 1b patients were performed during the evaluation. Adjustment could not be undertaken due to the lack of a control arm/common reference in the studies. The comparison, although highly uncertain due to exchangeability concerns, suggested that DCV+ASV may be less effective than DCV+SOF and did not appear to confer any safety benefits.

The sample sizes for the subgroups of genotype 1b patients in Study 4040 were very small, especially for treatment-experienced patients.

Indirect comparison of SVR rates for DCV+ASV and comparator treatment regimes in genotype 1b/1 patients

Comparison	DCV+ASV n/N % (95%CI)	Comparator n/N % (95%CI)	Absolute difference (95% CI)	Relative difference (95%CI)
DCV+ASV vs TVR+PR				
Treatment-naïve	180/203 ^a 88.7% (83.5%, 92.7%)			
Prior non-responders	70/87 ^c 80.5% (70.6%, 88.2%)			
DCV+ASV vs SOF+PR				
Treatment-naïve (non-cirrhotic)				
Prior non-responders (non-cirrhotic)				

CI = confidence interval; DCV = daclatasvir, PR = peginterferon and ribavirin; SOF = sofosbuvir; TVR = telaprevir

^a SVR12 (target not detected, TND) Study 7028, proportion of patients with cirrhosis 16%

^b ADVANCE trial, SVR24 (TND) genotype 1b patients, Telaprevir PI. Proportion of genotype 1 patients with cirrhosis 6%.

^c SVR24 (TND), Study 7026, proportion of patients with cirrhosis 13%. Study 7028 not included as 31% of patients had cirrhosis.

^d SVR24 (TND), Sitole et al (2013), a publication of meta-analysis of data from phase II and III trials. Pool results from three trials, includes both genotype 1a and 1b treatment-experienced patients, ~6% with cirrhosis.

^e SVR12 (target detected (TD) or TND), treatment-naïve from Study 7026; prior non-responders are pooled data Studies 7026 and 7028

^f SVR12 (TD or TND) Genotype 1b patients, Table 7.3.5-1, p91 of Study 4040 CSR

Source: Compiled during the evaluation

6.14 The European Medicines Agency (EMA) assessment report for daclatasvir stated that, in Study 7026, where daclatasvir was used in combination with asunaprevir, the presence of baseline NS5A Y93H viral polymorphism appeared to be associated with reduced susceptibility to daclatasvir and increased virological failure. This may have impacted on the applicability of study results to the proposed Australian PBS population. This was not an issue when daclatasvir was given in combination with sofosbuvir due to the potency of this combination and the barrier to resistance provided by sofosbuvir. The ESC noted the sponsor's response in the PSCR (p2) that 8 of 94 Australian GT1b patients carried the Y93H polymorphism which is consistent with the prevalence in the trial setting, and therefore the impact on observed effectiveness is likely to be small.

6.15 The PBAC considered the submission for ledipasvir and sofosbuvir (LDV/SOF) for the treatment of HCV Genotype 1 at the same meeting. The PBAC noted the SVR reported in the publication of Kowdley et al, 2014.

Comparative harms

6.16 The safety data from Studies 7026 and 7028 are presented below.

Summary of key on-treatment adverse events in Studies 7026 and 7028

Grading of AE	Study 7026	Study 7028		
	n with event/N (%)	All patients receiving DCV+ASV	n with event/N (%)	
	Total population		Treatment-naive ^a	
			DCV+ASV 12 weeks	Placebo 12 weeks
On-treatment AE	192/222 (86.5%)	547/645 (84.8%)	164/205 (80.0%)	74/102 (72.5%)
Treatment related AEs	127/222 (57.6%)	342/645 (53.0%)	-	-
Serious AEs ^b	13/ 222 (5.9%)	39/643 (6.1%)	7/205 (3.4%)	1/102 (1.0%)
Grade 3/4 AEs	37/222 (16.7%)	50/643 (7.8%)	9/205 (4.4%)	3/102 (2.9%)
Number discontinued	11/222 (5.0%)	10/643 (1.6%)	3/205 (1.5%)	0
Number died	0	0	0	0

AE = adverse event; ASV = asunaprevir; DCV = daclatasvir

^a AEs occurring during initial 12 week randomised phase of Study 7028

^b Defined as any untoward medical occurrence that at any dose resulted in death, was life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, or was an important medical event. On-treatment SAEs, which may not be related to treatments.

Source: Table 44 p123, Table 45, p 124, Table 46, p125 of the submission; p91, Study 7026 CSR; Appendix 6.5D p8282, Appendix 6.5C.1, p8269, Appendix 6.5N1, p8630, Table S.6.4A-1, p641 Study 7028 CSR

Benefits/harms

6.17 A summary of the comparative benefits and harms for DCV+ASV is presented below

Summary of comparative benefits and harms for DCV+ASV relative to no treatment

Patient group	Comparison	Benefits (SVR12)*	Harm**
Genotype 1b	for every 100 patients treated with DCV24+ASV24 in comparison to no treatment	<ul style="list-style-type: none"> Approximately 82-85 additional patients would be expected to achieve an SVR 	<ul style="list-style-type: none"> Approximately 6 additional patients would experience a serious AE Approximately 8-17 additional patients would experience a Grade 3/4 AE Approximately 2-5 additional patients would discontinue treatment due to AE
For the largest group seeking treatment: Genotype 1b, treatment naïve, non-cirrhotic patients			
	for every 100 patients treated with DCV+ASV for 24 weeks in comparison to ledipasvir and sofosbuvir for 8 weeks (based on Kowdley et al, 2014)	<ul style="list-style-type: none"> Approximately 11 fewer patients would be expected to achieve an SVR; 	<ul style="list-style-type: none"> Approximately 4 more patients would have a serious adverse event
	for every 100 patients treated with DCV+ASV for 24 weeks in comparison to DCV+SOF.	<ul style="list-style-type: none"> Approximately 11 fewer patients would be expected to achieve an SVR; 	<ul style="list-style-type: none"> Approximately 1 less patient would have a serious adverse event

* SVR = sustained virologic response, defined as undetectable HCV RNA at Week 12 after completion of treatment

** Based on on-treatment adverse events

DCV = daclatasvir; ASV = asunaprevir; AE = adverse event

Source: Compiled during the evaluation.

Clinical claim

- 6.18 The submission described DCV+ASV as superior in terms of both comparative effectiveness and comparative safety over TVR+PR in patients with genotype 1b HCV. This claim was not adequately supported in terms of the relative effectiveness of DCV+ASV compared to TVR+PR in treatment-naïve patients. The claim of superiority in terms of comparative safety is probably reasonable given the considerable adverse events associated with PR therapy.
- 6.19 With regard to the comparator considered appropriate by the PBAC, DCV+ASV was superior to 'no treatment' in terms of therapeutic effectiveness and inferior in terms of safety in both treatment-naïve and treatment-experienced patients with HCV genotype 1b.
- 6.20 The data indicated that DCV+ASV might be less effective and no safer than DCV+SOF, although there were concerns regarding the exchangeability of the study populations used in the unadjusted indirect comparison. DCV+SOF may also have advantages over DCV+ASV in patients with the baseline polymorphism that predicts increased virological failure.

- 6.21 The PBAC considered that the claim of superior comparative effectiveness and inferior comparative safety to no treatment was reasonable for GT1b naïve/experienced cirrhotic/non-cirrhotic patients.
- 6.22 The PBAC considered that non-inferiority between DCV24+ASV24 and LDV/SOF and between DCV24+ASV24 and DCV+SOF in Genotype 1b patients could not be supported with the data available to the Committee.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

Economic analysis

- 6.23 The economic model of DCV+ASV compared with no treatment, or active HCV treatment, was the same as that used to assess DCV+SOF, except that the population in the model was only for HCV genotype 1b. The summary of model structure and rationale is presented in PBAC documents of the DCV submission (item 5.06).
- 6.24 A summary of the key drivers of the model is presented below.

Key drivers of the DCV+ASV model

Description	Method/Value	Impact
Utility increment due to patients achieving SVR	0.05. Although this was used in some other HCV models, the PBAC considered this as a source of uncertainty when the listing of telaprevir was considered (Telaprevir PSD, November 2011 PBAC meeting)	High, favours DCV+ASV
Time horizon	49 years. This was longer than the PBAC recommendation (a 30 year time horizon) for HCV economic models in other HCV submissions (7.10, Item 5.17, PSD, July 2014 PBAC meeting).	Moderate, favours DCV+ASV
Transition probabilities	The model applied the transition probabilities used in the BCG report (2012). Many transition probabilities used in the BCG model were derived from older longitudinal studies and were likely to be overestimates (Telaprevir PSD, March 2012 PBAC meeting).	Moderate, favours DCV+ASV
SVR rate associated with DCV+ASV	Concerns remained regarding the applicability of these results to the proposed population.	unclear

ASV = asunaprevir; BCG = Boston Consulting Group; DCV = daclatasvir; HCV = hepatitis C virus; SVR = sustained virologic rate; PSD = public summary document.

Source: compiled during the evaluation

- 6.25 The submission presented an economic model of DCV+ASV compared with a mixture of active treatment and no treatment (67% of patients were assumed to be treated with TVR12+PR24/48 for genotype 1b, and the remaining 33% receiving no treatment). The Commentary presented separate cost-effectiveness analyses of DCV+ASV versus no treatment and versus TVR+PR. As noted above, the ESC noted that in the context of the growing preference for IFN-free therapy, the most relevant was comparator was no treatment.

- 6.26 The results of the economic evaluation for treatment-naïve HCV genotype 1b patients are summarised below.

Results of the DCV+ASV economic evaluation (versus no treatment)

	DCV24 + ASV24	No treatment	Increment
Costs	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
QALYs ^a	11.524	9.883	1.641
Incremental cost/extra QALY gained			\$ [REDACTED]
	DCV24 + ASV24	TVR12+PR24/48 ^b	Increment
Costs	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
QALYs ^a	11.524	11.434	0.090
Incremental cost/extra QALY gained			\$ [REDACTED]

ASV = asunaprevir; DCV = daclatasvir; HCV = hepatitis C virus; PR = peginterferon and ribavirin; QALY = quality-adjusted life year; TVR = telaprevir

^a Using a utility value of 0.60 for the F4(SVR) health state.

^b Assuming an SVR rate of 83.8% (SVR rate in genotype 1b patients in ADVANCE trial) for patients treated with TVR+PR

Source: Compiled during the evaluation from "DCV Economic Evaluation.xlsx" workbook

- 6.27 The concerns with regard to the economic evaluation of DCV+ASV included:
- The applicability of the SVR results from the DCV+ASV clinical studies to the Australian setting;
 - The exchangeability of the populations between the DCV+ASV and TVR+PR studies;
 - The time horizon of the model was longer than the PBAC had advised for other HCV models (49 years vs 30 years);
 - Transition probabilities between early health states of HCV infection (eg from mild to moderate HCV and from moderate HCV to compensated cirrhosis) were taken from older studies and likely to be overestimated. The transition probabilities in the National Institute of Health and Care Excellence (NICE) Health Technology Assessment report model of assessing HCV medicines were used in sensitivity analyses to address this issue; and
 - Utility increment as a consequence of having an SVR was assumed to be 0.05 in the submission. The assumption that patients in viral positive health states have a lower quality of life than those who achieve sustained virological response was explored in sensitivity analysis. Assumptions included no utility gain from achieving an SVR (see table below) and 0.041 as presented in the NICE report (PSCR).
- 6.28 During the evaluation additional sensitivity analyses were conducted. The results indicated that the model was most sensitive to the utility increment associated with achievement of SVR. Assuming no utility benefit due to SVR increased the ICER by 50%. Time horizon and transition probabilities had moderate impacts on the ICER. The use of 95% CIs of the SVR rate for treatment-naïve patients [83.5%, 92.7%] or the SVR rate for treatment-experienced patients reported for DCV+ASV in Study 7026 (80.5%) had limited effect on the ICER. When the model was respecified to include a time horizon of 30 years, transition probabilities sourced from the National Institute of Health and Care Excellence (NICE) Health Technology Assessment report model of assessing HCV medicines and no utility gain due to achieving an SVR, the ICER for genotype 1b patients tripled; increasing from a base case of \$15,000/QALY - \$45,000/QALY to \$45,000/QALY – \$75,000/QALY.

Results of sensitivity analyses performed during the evaluation (DCV+ASV versus no treatment) for genotype 1b patients

Variables	Assumptions	Incremental costs	Incremental QALYs	ICERs
Base case		\$ [REDACTED]	1.641	\$ [REDACTED]
Univariate analyses				
SVR rate associated with DCV+ASV (base case: 88.7%)	Upper limit of the 95% CI (92.7%)	\$ [REDACTED]	1.715	\$ [REDACTED]
	Lower limit of the 95% CI (83.5%)	\$ [REDACTED]	1.545	\$ [REDACTED]
Treatment-experienced patient in the model (base case: not included)	SVR rate of 80.5% (as reported in treatment-experienced patients in Studies 7026 and 7028)	\$ [REDACTED]	1.490	\$ [REDACTED]
	Upper limit of the 95% CI (88.2%)	\$ [REDACTED]	1.632	\$ [REDACTED]
	Lower limit of the 95% CI (70.6%)	\$ [REDACTED]	1.306	\$ [REDACTED]
Time horizon (base case: 49 years)	30 years (PBAC recommendation)	\$ [REDACTED]	1.430	\$ [REDACTED]
Transition probabilities	Using inputs from the NICE model ^a	\$ [REDACTED]	1.358	\$ [REDACTED]
Utilities (base case: sourced from Wright et al 2006)	Using Townsend utility values	\$ [REDACTED]	1.145	\$ [REDACTED]
	Using Townsend utility values, but assuming a 0.05 utility gain due to achieving SVR	\$ [REDACTED]	1.518	\$ [REDACTED]
	Using Wright utility values, but assuming no utility increment due to achieving SVR	\$ [REDACTED]	1.026	\$ [REDACTED]
Multivariate analyses				
Time horizon +Transition probabilities	30 years Using inputs from the NICE model ^a	\$ [REDACTED]	1.193	\$ [REDACTED]
Time horizon +Transition probabilities +Utilities	30 years Using inputs from the NICE model ^a Using Townsend utility values	\$ [REDACTED]	0.758	\$ [REDACTED]
Time horizon +Transition probabilities +Utilities	30 years Using inputs from the NICE model ^a Assuming no utilities increment due to SVR	\$ [REDACTED]	0.604	\$ [REDACTED]

ASV = asunaprevir; CI = confidence interval; DCV = daclatasvir; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; SVR = sustained virologic response

^a Using the transition probabilities as presented in the commentary and combining the F0 health state with the F1 health state and the F2 health state with the F3 health state

Source: Sensitivity analyses conducted during the evaluation, using the corrected utility value of 0.60 for the F4(SVR) health state.

- 6.29 The ESC noted the sensitivity analysis presented in the PSCR (p5, presented below), resulting in an ICER of \$15,000/QALY - \$45,000/QALY. In addition, incorporating these assumptions addressed in the PSCR as well as using transition probabilities in the NICE model, the ICER was \$15,000/QALY - \$45,000/QALY.

Revisions to base case estimates for DCV + ASV vs. no treatment in a HCV GT1b population (PSCR)

Variable tested	Value	Incremental cost	Incremental QALY	ICER
Base case (submission) vs. no treatment		\$ [REDACTED]	1.7606	\$ [REDACTED]
Correcting utility value for F4(SVR)	0.72 to 0.60	\$ [REDACTED]	1.6408	\$ [REDACTED]
Adjustment for polymorphism prevalence and SVR rate	8.5% 42% SVR	\$ [REDACTED]	1.5679	\$ [REDACTED]
Reduced utility increment associated with SVR as per NICE assessment	0.05 to 0.041	\$ [REDACTED]	1.4408	\$ [REDACTED]
Reduce model duration to 30 years	49 to 30 years	\$ [REDACTED]	1.2454	\$ [REDACTED]
Sensitivity analysis incorporating evaluator's suggested changes	-	\$ [REDACTED]	1.2454	\$ [REDACTED]

6.30 The ESC made the following general comments about the direct-acting antivirals (DAA) for the treatment of Hepatitis C:

- The most appropriate scenario for decision-making in the Australian context was the treatment of patients infected with Genotype 1 and 3 hepatitis C virus compared to no treatment. This reiterated the view of the PBAC at the July 2014 Meeting. (Sofosbuvir PSD, July 2014). The ESC considered that the treatments (submitted to the PBAC March 2015 meeting) were clinically effective in providing a SVR12 against hepatitis C. The ESC also considered that over time GT1 and GT3 treatment naïve non-cirrhotic patients are likely to become the predominant treatment populations, and therefore ICERs for this group should be most influential for decision-making.
- In the economic analysis, when 100% of treated patients were assumed to be cirrhotic, the ICER was lower than when 100% of treated patients were assumed to be non-cirrhotic. Despite a smaller treatment effect (i.e. a lower SVR), the ESC noted that this ICER difference was driven by the delay of outcomes such as decompensated cirrhosis, hepatocellular carcinoma and mortality which generally were more likely to occur, and to occur sooner, in an untreated cirrhotic population.
- In the economic models, it was more reasonable to assume that a cirrhotic patient with a SVR still had cirrhotic disease, and therefore would likely have an on-going risk of complications and mortality closer to that of an untreated cirrhotic patient than to that of the background population. On the other hand, a SVR in a patient without cirrhosis is likely to avoid liver complications and associated disease due to viral eradication.
- The listing of the new treatment for hepatitis C should not be restricted by stage of hepatic fibrosis. However in clinical practice, the ESC considered that higher risk patients, such a patients with cirrhosis, are likely to be treated sooner following listing of interferon-free treatments. The ESC noted preliminary data from the ongoing, longitudinal, observational HCV-TARGET study ([clinicaltrials.gov NCT01474811](http://clinicaltrials.gov/NCT01474811)) showed that 45-60% of patients treated with interferon-free regiments were cirrhotic. (http://www.natap.org/2014/AASLDEASL/AASLDEASL_01.htm). However, the ESC considered that with the availability of highly effective and well-

tolerated therapy, over time the predominant treatment population would be treatment naïve GT1 and GT3 patients without cirrhosis.

- A consequence of this treatment pattern would be the rapid reduction of the pool of infected patients with cirrhosis. The ESC noted that all submissions assumed in the economic analysis that the proportion of patients with cirrhosis was greater than the figure of 5.9% (distribution of hepatic fibrosis stage F4) cited in the Recommendations from the Australian Liver Association (ALA). While the proportion of patients with cirrhosis would not reach zero, due to the current system capacity, the ESC considered that the assumption of a static and high prevalence of cirrhotic patients in the analysis favours the treatment arm in the medium to long term, and does not reflect the cost-effectiveness of overall treatment in the short term following the listing of these treatments. The ESC considered that it was more informative to present the ICER for non-cirrhotic and cirrhotic patients separately to see the extremes of the cost-effectiveness.
- During the discussion, the ESC recalled the consideration of sofosbuvir at the July PBAC 2014 meeting. The ESC noted that the PBAC recalled that for the submissions for boceprevir and telaprevir the ICER range accepted was \$15,000- \$45,000/QALY. The PBAC considered that trying to value sofosbuvir with a weighted ICER was inappropriate when the ICER for some treatment groups was substantially higher than this range. The PBAC was also concerned that the weightings that underpin the weighted value for each treatment group, were uncertain due to the number of assumptions made about the proportion of patients with prior treatment/cirrhosis/IFN eligibility and genotype. (PSD, July 2014). In addition, the ESC noted that a weighted ICER should be generated by weighting costs and weighting benefits, before calculating the ratio.
- The ESC noted the very large opportunity cost of the new medicines for the treatment Hepatitis C, if listed at the price proposed. A consequence of a significant opportunity cost to the health care system is the potential for reduced access to future cost-effective medicines. The ESC considered that in this situation, it would be appropriate and necessary for the PBAC to expect that the ICERs that would define potentially acceptable cost-effectiveness should be at the lower end of the range previously accepted for interventions for this disease.

6.31 The PBAC noted the cost-effective analysis presented in the submission. The PBAC agreed with the revised base case presented in the ESC. The PBAC disagreed with the sponsor and considered that a 30 year time horizon was appropriate. The PBAC noted that ICER may be higher if the more conservative transition probabilities from the NICE assessment raised in the Commentary were applied to the model. In addition, the PBAC noted the other items, at the March 2015 meeting, modelling the cost-effectiveness of HCV treatment, using inputs and assumptions that the PBAC considered to be more appropriate for this disease.

6.32 Overall, the economic model presented in the submission favoured asunaprevir in combination with daclatasvir and that applying more conservative inputs or scenarios increased the ICERs/QALY to a range higher than the PBAC considered cost-effective for the treatment of CHC.

6.33 The PBAC noted the SVR following treatment with LDV/SOF reported in the publication of Kowdley et al, 2014 and following treatment with DCV+ SOF presented in the submission. The PBAC considered that ASV with DCV had not established

non-inferior efficacy compared to LDV/SOF or DCV+SOF, recommended at the same PBAC meeting. Though the more appropriate economic approach, the PBAC considered cost minimisation of ASV with DCV compared to LDV/SOF or DCV+SOF was not supported with the data provided in the submission.

Drug cost/patient/course: \$ [REDACTED] (DCV+ASV).

- 6.34 Cost of daclatasvir: \$ [REDACTED] for a 24 week course.
 Cost of asunaprevir: \$ [REDACTED] for a 24 week course.
 Patients only receive one 24 week course of treatment.

Estimated PBS usage & financial implications

- 6.35 The submission was considered by the Drug Utilisation Sub-Committee.
- 6.36 The following estimates of PBS usage and financial implications were presented in the submission. At year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be less than \$10 million per year.

Estimated net financial cost/year to the PBS/RPBS

	Year 1	Year 2	Year 3	Year 4	Year 5
Cost of DCV+ASV					
Number of patients	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total cost	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Patient co-payments	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Total cost to PBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Cost off-sets					
Number of patients	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total cost	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Patient co-payments	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Total cost to PBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost/year					
Additional patients treated	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Net total cost	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net patients co-payments	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Net cost to the PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

ASV = asunaprevir; DCV = daclatasvir; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

Source: Table 149, p294 of the submission; Excel workbook "Section E DCV Primary Analysis" and Commentary on the Main Submission Table E(II).4.1 p162

- 6.37 DUSC considered that in the context of prescribing continuing through tertiary specialist settings, the estimated treated population is reasonable. However, DUSC considered that should DCV+ASV be the only interferon-free regimen, the treated

population could be greater if genotype 1b may become a comparatively larger portion of patients who are actively treated.

- 6.38 DUSC considered that the cost off-sets for substituted treatment were overestimated. The submission’s assumption of a 10% annual growth in the treatment rate for the existing interferon-containing regimens until 2017 with a reduction in the rate to 2.6% over the remaining forward estimates period was considered to be unlikely because patients are deferring treatment in anticipation of the availability of oral, interferon-free regimens.
- 6.39 The net cost to government for the proposed listing of DCV+ASV is summarised in the following table.

Estimated net financial implications for the Government health budget

	Year 1	Year 2	Year 3	Year 4	Year 5
Net cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to MBS	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Net cost to Government health budget	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme
 Source: Table 157, p302 of the submission and Commentary on the Main Submission Table E(II).5.3 p164.

- 6.40 The redacted table above shows that at year 5, the net cost to the PBS/RPBS is forecast to be less than 10 million per year and the net cost to the Government health budget would be less than \$10 million per year.
- 6.41 The submission claimed that DCV+ASV will reduce costs associated with on-treatment surveillance, psychiatric follow-up and thyroid function tests compared to current treatment regimens. DUSC noted that the claimed net savings to the MBS were highly uncertain as the costing assumptions could not be verified during the evaluation.
- 6.42 The PBAC noted the DUSC advice on the item and on the treatment of patients with CHC generally. The PBAC was of the view that the DUSC estimates for patients with any HCV genotype likely to be treated were appropriate. At year 1, the estimated number of patients treated with any HCV genotype was [REDACTED]. At year 5, the estimated number of patients treated was [REDACTED] for any genotype.

Financial Management – Risk Sharing Arrangements

- 6.43 If daclatasvir is listed for use in combination with both asunaprevir and sofosbuvir, the submission proposed that daclatasvir would be listed at a published DPMQ of \$ [REDACTED], with a rebate applied to the proportion of daclatasvir dispensed for use in combination with asunaprevir to reduce the effective DPMQ to \$ [REDACTED]. The DPMQ of daclatasvir for the proportion dispensed for use in combination with sofosbuvir would remain at \$ [REDACTED], with no rebate applied. If only DCV+ASV is listed, the proposed DPMQ of daclatasvir was \$ [REDACTED], with no rebate.

7 PBAC Outcome

- 7.1 The PBAC rejected the submission for the Authority Required (Streamlined) listing for asunaprevir (in combination with daclatasvir) for the treatment of chronic hepatitis C Genotype 1b because the treatment was clinically not non-inferior to treatment with ledipasvir and sofosbuvir (LDV/SOF) or daclatasvir + sofosbuvir (DCV+SOF) for treatment naive patients with Genotype 1b.
- 7.2 The PBAC reiterated that the Committee recognised that new treatments of HCV resulted in high rates of sustained virological response, where the HCV virus could not be detected in the blood of patients 12 weeks after treatment commenced. The PBAC noted that the large number of comments and presentations from patients, health care professionals and organisations highlighted the benefits of the availability of new treatments, particularly IFN-free regimens.
- 7.3 The PBAC recalled the discussion at the Stakeholder meeting (February 2014) about the setting patients should be treated in. The PBAC considered that it was appropriate that the new all oral treatment to be listed in the General Schedule, to facilitated the longer term objectives for access to treatment, increase treatment rates and outcomes and acknowledging initiatives such as The Fourth National Hepatitis C Strategy 2014-2017 and NSW Hepatitis C Strategy 2014-2020 to support a greater role of primary care in the prescribing and monitoring of the newer generation of antivirals, that have reduced side effects and more simplified dosing schedules. The PBAC noted that treatment of patients would initially remain in tertiary settings but expand as clinician experience grows.
- 7.4 The submission proposed the current active treatments as the comparator. The PBAC reiterated their view that the appropriate comparator, when the submission was lodged, was 'no treatment', in view of the broader context of infected individuals whose treatment preference is interferon-free therapies. Following the recommendation to list sofosbuvir-containing regimens, the PBAC considered that these sofosbuvir-containing regimens were the most appropriate comparators for the consideration of other all oral HCV treatments, given that LDV/SOF and SOF are likely to become the standard of care for almost all patients treated for CHC.
- 7.5 The PBAC considered that the claim of superior comparative effectiveness and inferior comparative safety to no treatment was reasonable for GT1b naïve or experienced cirrhotic or non-cirrhotic patients.
- 7.6 The PBAC considered that non-inferiority between asunaprevir in combination with daclatasvir and ledipasvir/ sofosbuvir and between asunaprevir in combination with daclatasvir and daclatasvir in combination with sofosbuvir in Genotype 1b patients was not supported by the data available to the Committee.
- 7.7 The PBAC accepted the structure of the economic model presented in the submission but considered that the base case should be respecified to that suggested by the ESC. Overall, the economic model presented in the submission favoured asunaprevir in combination with daclatasvir and that applying more conservative inputs or scenarios increased the ICERs/QALY to a range higher than the PBAC considered cost-effective for the treatment of CHC.

- 7.8 The PBAC noted the DUSC advice on the item and on the treatment of patients with CHC generally. The PBAC was of the view that the DUSC estimates for patients with any HCV genotype likely to be treated were appropriate. At year 1, the estimated number of patients treated with any HCV genotype was 6,660. At year 5, the estimated number of patients treated was 15,000 for any genotype.
- 7.9 The PBAC noted that this submission is eligible for an Independent Review.
- 7.10 The PBAC wished to advise the Minister that:
- While interferon-free oral direct acting antiviral (DAA) agents provide safe and effective treatment options for patients with CHC, there is a substantial opportunity cost associated with the potential listing of these medicines. The lower estimate of this opportunity cost is more than \$3 billion over 5 years, at the prices proposed in the submissions. Given this large opportunity cost, the cost of a course of treatment should be set irrespective of the duration, and that other pricing policies be considered.
 - The impact of the new antivirals on patients currently infected has been modelled by Sievert et al. (2014). This modelling shows that the number of people with chronic hepatitis C (CHC) will be reduced by 60% in 2030 compared to the base case of current treatment. The assumptions in the model include up to 13,500 people (including all fibrosis stages) are treated annually by 2018 and the DAA agents are expected to have rates of sustained virologic response (measured at 12 weeks, SVR12) up to 90% for genotype 1 and 80% for genotype 3 by 2016. The analyses accounted for mortality but did not consider re-infection.
 - Advice from the Australian Liver Association (ALA) indicated that of the estimated 233,000 people living with Hepatitis C virus (HCV), 193,000 patients have been diagnosed. Listing of oral DAA agents may increase public and clinician awareness of the disease potentially leading to increased testing and diagnosis.
 - The DUSC analysis shows that approximately 60 000 patients would be treated over 5 years, based on treatment targets in the Fourth National Hepatitis C Strategy 2014-2017, together with the advice from the ALA and February 2014 Stakeholder meeting (New oral antivirals for the Treatment of Hepatitis C). However, it is not clear how many people living with CHC will seek treatment, particularly if patients have to be seen in specialist liver clinics or wait for a referral to a liver clinic. Prescribing is likely to continue to be delivered through specialist clinics in the short-term until clinicians in other settings have learned how to use the DAA agents. Patients may still be required to go through the hospital system as part of their clinical management, which could be a limiting factor to uptake.
 - Given the very large opportunity cost, one option would be to restrict access to treatment to those with the highest clinical need. The PBAC considered that it was inappropriate to restrict access, given the likely benefit of the DAA agents across the full spectrum of patients with CHC, from those with early disease to those patients with existing liver cirrhosis and severe portal hypertension, decompensated liver disease, or patients post liver transplant. The benefits in terms of avoidance or delay of decompensated cirrhosis, hepatocellular carcinoma and morbidity are likely to be seen earlier in the most severely ill, but population benefits, such as reduction in transmission of the disease, are likely to occur with wide access to treatment.

This and other benefits may be also realised via other community-based programmes and strategies, such as those described in the Fourth National Hepatitis

C Strategy 2014-2017.

- The high response (sustained virologic response measured at 12 weeks, SVR12) observed in the clinical trials may only be realised if the adherence of patients in Australia to treatment is similar to those in the clinical trials. While there is a patient preference for shorter treatments, and new shorter treatment regimens are currently being tested, for some patients, 24 weeks of treatment are necessary. Therefore it is critical that appropriate prescribing education be put in place to ensure that the benefits to the Australian community are maximised.
- The treatment landscape of HCV treatment is changing rapidly, as new DAA agents or new combinations of DAA agents become available and treatment guidelines are regularly updated. It is likely that new DAA agents will be produced over the next 2 to 3 years that may further increase treatment options.
- In this context, the current treatment for CHC, such as peginterferon and ribavirin alone and in combination with telaprevir, boceprevir or simeprevir, are no longer cost-effective as currently listed especially given the higher rate of adverse effects observed in clinical practice for some treatment combinations compared to those observed in the clinical trials. The Minister may wish to review the listing of these products. The PBAC advised the Department to bring this consideration to the attention of the sponsor of these products. The Commonwealth currently pay approximately \$87 million for these treatments.

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

The Sponsor had no comment.