

## 5.06 DACLATASVIR 60mg or 30mg, tablets; Daklinza®; Bristol-Myers Squibb

### 1 Purpose of Application

- 1.1 The submission requested a Section 85 Authority Required (STREAMLINED) listing for daclatasvir for treatment of chronic hepatitis C virus (HCV) infection, in combination with sofosbuvir.

### 2 Requested listing

- 2.1 The requested listing was:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
DACLATASVIR			Daklinza Bristol-Myers Squibb
Tablet 60mg, 28	3	0	
Tablet 30mg, 28	3	0	
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	<p><u>60mg tablet</u> 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</p> <p><u>30mg tablet</u> Patient must have compensated liver disease requiring dose adjustment due to CYP3A4 inhibitors or inducers, The treatment must be limited to a maximum duration of 12 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 sofosbuvir<sup>a</sup></p>		
Population criteria	Patient must be 18 years or older		

<sup>a</sup> The 30mg tablet is for use in patients receiving concomitant therapies which strongly inhibit the CYP3A4 enzyme; asunaprevir is contraindicated in these patients.

- 2.2 The current listings for the protease inhibitors are Section 100 Highly Specialised Drug Program.
- 2.3 The submission proposed a treatment regimen of daclatasvir in combination with sofosbuvir for 12 weeks (DCV12+SOF12) for patients with all HCV genotypes. This duration was consistent with the draft daclatasvir Product Information (PI). However the proposed restriction for daclatasvir 60mg tablet stipulated a maximum treatment duration of 24 weeks but the maximum quantity (3x28) and lack of repeats in the

proposed listing only allowed for 12 weeks supply of daclatasvir. The submission noted that the proposed listing of daclatasvir when combined with asunaprevir allows for 24 weeks supply of daclatasvir (see item 5.03 of the March 2015 meeting) Patients may access 24 weeks of DCV+SOF via that listing. However, this problem with the restriction would be addressed if two PBS listings were proposed for each of the daclatasvir combinations (ie with SOF or ASV). The ESC noted that the updated draft PI (pg 24), provided with the PSCR, stated 'Consider adding ribavirin to the DAKLINZA/sofosbuvir 12-week regimen or prolonging treatment duration to 24 weeks for patients with cirrhosis or with other negative prognostic factors such as prior treatment experience (eg, protease inhibitor, peginterferon alfa and ribavirin)'. The ESC noted that the proposed restriction does not explicitly exclude combination of DCV+SOF with RBV which might not be cost-effective.

- 2.4 Listing was sought on a cost effectiveness basis of daclatasvir in combination with sofosbuvir for 12 weeks compared to a mixture of no treatment and active treatment.
- 2.5 The DUSC considered that it is uncertain whether and when the current model of care involving specialist treatment centres will change to a greater involvement of primary care in HCV prescribing with a subsequent broader access to treatment.
- 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 CHC over time.
- 2.7 General schedule listing is in line with 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.
- 2.8 The PBAC considered that the Department in consultation with clinical experts should explore whether primary care prescribing should be available to practitioners who have gained accreditation (as occurs currently for Section 100 prescribing) or in a Share Care Model (namely, in consultation with a clinician with experience of prescribing treatment for CHC, such as a hepatologist or infectious disease physician). The PBAC considered that an Authority Required listing was appropriate, but whether this Authority is written, telephone or streamlined remains to be finalised. The conditions of the listing would also depend on the final registered Product Information.

*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 was made under TGA/PBAC Parallel Process. The clinical evaluation report for daclatasvir was provided on 30 January 2015. The TGA delegate's overview was provided on 3<sup>rd</sup> March 2015, and would be considered at the ACPM meeting to be held on 15<sup>th</sup> May 2015.
- 3.2 Daclatasvir had not been previously considered by the PBAC.

### **4 Clinical place for the proposed therapy**

- 4.1 HCV infection is a major cause of chronic liver disease. The cycle of viral reproduction within hepatic cells and the response by the host immune system to the infection results in damage to the host's liver. Chronic infection can lead to scarring of the liver and ultimately to cirrhosis. In some cases, patients with liver cirrhosis develop liver failure, liver cancer or life-threatening oesophageal and gastric HCV. Currently, Genotype 1 or Genotype 3 HCV account for 88-92% of infections in Australia.
- 4.2 Currently, the PBS reimburses direct acting antivirals (DAAs), including boceprevir, telaprevir and simeprevir (three HCV NS3/4A inhibitors, all of which must be used in combination with PR), for the treatment of HCV genotype 1. In addition, the PBS reimburses peginterferon alfa-2a or alfa-2b in combination with ribavirin for the treatment of genotypes 1-6 HCV.
- 4.3 The proposed treatment regimen of DCV+SOF provides an all-oral, interferon and ribavirin free option for HCV patients of all genotypes, regardless of their previous treatment history. Daclatasvir is an oral DAA and a pan-genotypic inhibitor of NS5A, a multifunctional protein that is an essential component of the HCV replication complex. Sofosbuvir is also an oral DAA that can be used to treat HCV genotypes 1-6. The dose regimen proposed in the submission was daclatasvir 60mg once daily, in combination with sofosbuvir 400mg once daily with food, for 12 weeks.

### **5 Comparator**

- 5.1 The submission nominated a protease inhibitor plus PR as the main comparator for DCV+SOF in HCV genotype 1 patients, and PR as the main comparator in HCV genotype 2-6 patients. These may be appropriate comparators for those patients who are currently seeking active HCV treatment. However many HCV patients are not undertaking therapy because current interferon-based therapies are often not tolerated well. At the July 2014 PBAC meeting the Committee considered that the appropriate comparator should be 'no treatment' (Paragraph 7.5, 5.17 Sofosbuvir, PSD – July 2014 PBAC meeting).
- 5.2 The ESC noted that in the context of the growing preference for IFN-free therapy, the most relevant comparator was no treatment.

## **6 Consideration of the evidence**

### **Sponsor hearing**

6.1 There was no hearing for this treatment combination.

### **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<sup>®</sup>) 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.

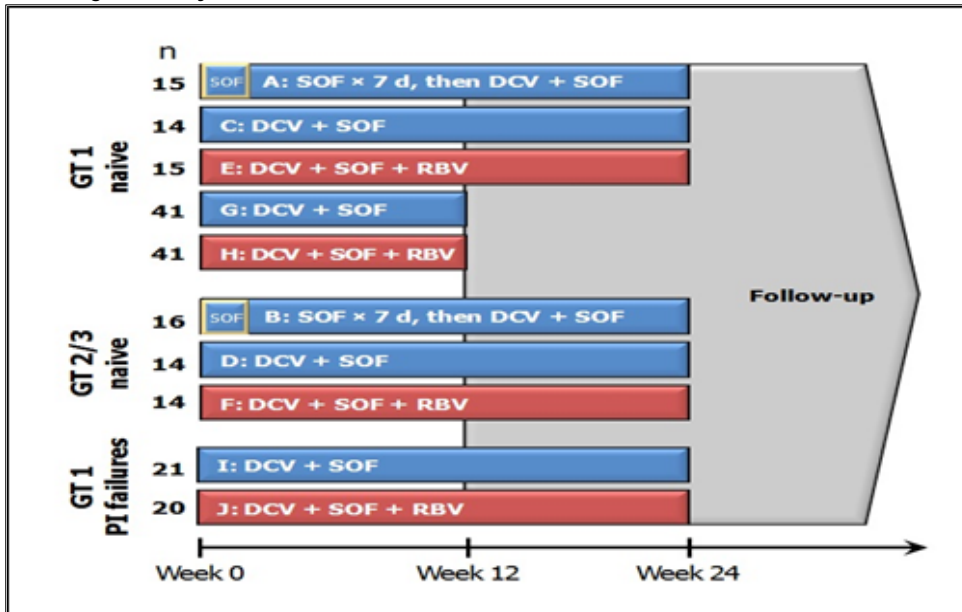
6.4 The PBAC noted and welcomed this input.

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

**Clinical study**

6.5 The submission was based on one open-label randomised trial (Study 4040) comparing various dose regimens of DCV+SOF±R in treatment-naïve patients with genotype 1, 2 and 3 HCV as well as treatment-experienced patients with genotype 1 HCV. Study 4040 was an open-label study that included 10 treatment groups (Groups A-J). The study design for Study 4040 is presented in the figure below. As there was no relevant comparator arm in this open-label study, it was considered as a non-comparative study for the purposes of the evaluation.

The design of Study 4040



d = days; DCV = daclatasvir; GT = genotype; PI = protease inhibitor; RBV = ribavirin; SOF = sofosbuvir;  
Source: Figure 18, p72 of the submission.

6.6 Details of the study presented in the submission (Study 4040) and the details of other trials provided in the PSCR are provided in the table below.

**The study and associated reports presented in the submission**

Study ID	Protocol title/ Publication title	Publication citation
DCV+SOF		
Study 4040	Final Clinical Study Report for Study AI444040: Parallel open-label, randomized study to evaluate the safety, pharmacokinetics, and pharmacodynamics of PSI-7977 in combination with BMS-790052 with or without ribavirin in treatment-naïve subjects chronically infected with hepatitis C virus genotypes 1, 2, or 3. Sulkowski, M.S. et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection."	Date: September 2013  New England Journal of Medicine 2014; 370 (3): 211-221.
ALLY1 ALLY2 ALLY3 (information provided in the PSCR, not evaluated in the Commentary)	ALLY 1 (AI444-215) was a phase 3, open-label study of DCV + SOF for 12 weeks in patients with cirrhosis or post-liver transplant.  ALLY2 (AI444-216) was a phase 3, randomized, open-label study of DCV + SOF for 8 or 12 weeks in treatment naïve and treatment experienced patients with HIV co-infection.  ALLY 3 (AI444-218) was a phase 3, open-label study of DCV + SOF for 12 weeks in treatment naïve and treatment experienced patients with HCV GT 3 infection. Nelson, D.R. et al.	Hepatology (2015). Accepted online ahead of print: <a href="http://onlinelibrary.wiley.com/doi/10.1002/hep.27726/pdf">http://onlinelibrary.wiley.com/doi/10.1002/hep.27726/pdf</a> .

HCV = hepatitis C virus

Source: Table 23, p71 of the submission and page 2 of the PSCR

- 6.7 Study 4040 was a non-comparative study. Other key features are summarised in the table below.

**Key features of the included evidence**

Study	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
<b>Non-comparative study</b>						
Study 4040	211	Single arms of R, OL 24 weeks after last dose	Medium <sup>a</sup>	GT 1,2 3 treatment-naïve and G1 treatment- experienced <sup>b</sup>	SVR	Used

OL=open label; R=randomised; GT = genotype; SVR = sustained virologic response

<sup>a</sup> Given the relevant comparator is 'no treatment', the assessment of SVR is at low risk, but the assessment of safety data may be at a high risk due to the open label design.

<sup>b</sup> patients with documented cirrhosis have been excluded from the study.

Source: compiled during the evaluation

6.8 The submission requested that DCV12+SOF12 be listed for all HCV genotypes regardless of previous treatment history or cirrhosis status. No evidence relating to the therapeutic effectiveness of DCV+SOF was provided in the submission for the following population subgroups:

- Patients with documented cirrhosis;
- Treatment-naïve patients with genotypes 4-6 HCV;
- Treatment-experienced patients with genotypes 2-6 HCV;
- Patients with HCV and human immunodeficiency virus (HIV) or hepatitis B virus (HBV) co-infection.

6.9 Three additional clinical trials are currently being conducted:

- one assessing DCV12+SOF12 in both treatment-naïve and treatment-experienced patients with genotype 3 HCV infection (ALLY 3);
- one assessing DCV12+SOF12+R12 in cirrhotic or post-transplant patients (ALLY 1); and
- one assessing DCV+SOF for either 8 or 12 weeks in patients with genotype 1-6 HCV and HIV co-infection (ALLY 2).

The submission states that the SVR12 data from ALLY 3 is likely to be available in late 2014, with the results of the other two studies expected in early 2015. The PSCR (p2) provided limited information about the results of ALLY1-3. The ESC noted the additional data provided for GT3 patients for ALLY-3 and publication: Nelson, D.R. et al. Hepatology (2015). Accepted online ahead of print: <http://onlinelibrary.wiley.com/doi/10.1002/hep.27726/pdf>.

### Comparative effectiveness

6.10 The sustained virologic response (SVR) rate across each treatment regimen in Study 4040 is given in the table below.

Results of sustained virologic response rate across the treatment regimens in Study 4040

Treatment groups	GT	N	Treatment regimen/duration	SVR12 (TND) <sup>a</sup> , n/N % (95%CI)	SVR 24 (TND) <sup>a</sup> , n/N % (95%CI)
<b>Treatment-naïve</b>					
G	1	41	DCV12+SOF12	41/41 100% (91.4%, 100%) <sup>b</sup>	39/41 95.1% (83.5%, 99.4%)
H	1	41	DCV12+SOF12+R12	39/41 95.1% (83.5%, 99.4%)	38/41 92.7% (80.1%, 98.5%)
B	2/3	16	SOF lead-in Week 1 (SOF1)+ DCV23+SOF23	14/16 <sup>c</sup> 87.5% (61.7%, 98.4%)	14/16 <sup>c</sup> 87.5% (61.7%, 98.4%)
D	2/3	14	DCV24+SOF24	13/14 <sup>d</sup> 92.9% (66.1%, 99.8%)	14/14 <sup>d</sup> 100% (76.8%, 100%)
F	2/3	14	DCV24+SOF24+R24	12/14 85.7% (57.2%, 98.2%)	13/14 92.9% (66.1%, 99.8%)
<b>Treatment-experienced</b>					
I	1	21	DCV24+SOF24	21/21 100% (83.9%, 100%) <sup>b</sup>	NR
J	1	20	DCV24+SOF24+R24	19/20 <sup>h</sup> 95.0% (75.1%, 99.9%)	NR

GT = genotype; CI = confidence interval; DCV = daclatasvir; NR = not reported; R = ribavirin; SOF = sofosbuvir; SVR = sustained virologic response; TND = target not detected

*Public Summary Document – March 2015 PBAC Meeting*

The numbers following each drug indicate the number of weeks treated;

<sup>a</sup> SVR defined as undetectable HCV RNA

<sup>b</sup> 1-sided 97.5% confidence interval

<sup>c</sup> In Group B, 1 patient had viral breakthrough and 1 patient had relapse

<sup>d</sup> In Group D, the SVR 12 (TD or TND) was 14/14 (100%)

Note: all other discrepancies between SVR12 and SVR 24 were due to missing data.

The exact binomial confidence intervals were calculated during the evaluation.

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

- 6.11 The SVR rate was high in all treatment groups. It should be noted that hard-to-treat patients, such as those with documented cirrhosis or treatment-experienced patients with HCV genotypes 2 to 6, were not included in the study. In addition, the sample size in many patient subgroups was small and may not accurately estimate of the magnitude of the clinical benefit. The ESC noted the numerically lower SVR rate of DCV24+SOF24 +/- RBV among treatment naïve GT2/3 patients, compared with the SVR rate of DCV12-24+SOF12-24 +/- RBV for treatment naïve GT1 patients.
- 6.12 There was no evidence for the proposed treatment regimen (DCV12+SOF12) in treatment-naïve genotype 2 to 6 HCV and treatment-experienced patients. Twenty-four weeks of treatment was given to genotypes 2 and 3 treatment-naïve and genotype 1 treatment-experienced patients in Study 4040. As the viral susceptibility to daclatasvir is lower in genotypes 2 and 3 compared to genotypes 1 and 4, it may not be appropriate to assume that 12 weeks of treatment will be as effective in patients with these genotypes as it is in genotype 1 patients. Given the proposed listing did not preclude 24 weeks of treatment with DCV+SOF, DCV24+SOF24 might be used in clinical practice if listed.
- 6.13 The ESC noted that results from ALLY-3 open label trial of DCV/SOF12 for treatment naïve and experienced patients with GT3 became available after submission. In ALLY-3, SVR rates for DCV+SOF12 were high among naïve (73/75) and experienced (32/34) GT3 patients without cirrhosis. However, among the small number of GT3 patients with cirrhosis, SVR was low among both naïve (11/19) and experienced (9/13) patients. The ESC also noted the unpublished point estimates of efficacy from ALLY-1 and ALLY-2 provided in confidence in the PSCR and considered that the data provided no additional certainty about the efficacy of DCV+SOF12 among GT1 and GT3 cirrhotic patients.
- 6.14 The submission presented the results of two, matching-adjusted, indirect comparisons (MAICs), firstly between DCV+SOF and TVR+PR and, secondly, between DCV+SOF and SOF+PR, in treatment-naïve patients with genotype 1 HCV. The results are reported below. For all other patient subgroups, the submission only provided a 'qualitative indirect comparison' of DCV+SOF and the comparators nominated in Section B; no statistical analyses were provided. The SVR rates presented for the comparators in both the MAICs and the 'qualitative' comparisons were biased, as they included cirrhotic patients, in contrast to Study 4040 which excluded this hard-to-treat subgroup. Subjects in Study 4040 and those in the comparator trials were comparable in terms of some prognostic factors, for example age and baseline RNA level. Data on other baseline characteristics, such as time duration between diagnosis and treatment were not available in the submission.

Indirect comparison of DCV+SOF and comparator treatment regimes in treatment-naïve genotype 1 patients, as presented in the submission

Comparison	Outcome	DCV+SOF <sup>a</sup> n/N, %	Comparator n/N, %	Absolute difference (95% CI)
<b>DCV+SOF vs TVR+PR</b>				
Unweighted <sup>g</sup>	SVR24 <sup>b</sup>		73.0% <sup>c</sup>	
Weighted <sup>h</sup>	SVR24 <sup>b</sup>		73.0%	
<b>DCV+SOF vs SOF+PR</b>				
Unweighted <sup>g</sup>	SVR12 <sup>d</sup>		89.6% <sup>f</sup>	
Weighted <sup>i</sup>	SVR12 <sup>d</sup>		89.6% <sup>f</sup>	

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

<sup>a</sup> Group G, treatment-naïve genotype 1 patients treated with DCV12+SOF12

<sup>b</sup> Defined as undetectable HCV RNA at follow-up Week 24

<sup>c</sup> Sourced from ADVANCE and ILLUMINATE. Includes 9% cirrhotic patients.

<sup>d</sup> Defined as HCV RNA <25IU/mL at follow-up week 12

<sup>f</sup> Sourced from NEUTRINO trial, genotype 1. Includes ~16% cirrhotic patients.

<sup>g</sup> Using SVRs reported in Study 0404

<sup>h</sup> Patients in Study 4040 were weighed by their estimated odds of enrolment in Trials ADVANCE and ILLUMINATE as opposed to enrolment in Study 4040 in an attempt to balance baseline characteristics between trial subjects when comparing the treatment effect of DCV+SOF vs TVR+PR. This analysis could not be verified during the evaluation.

<sup>i</sup> Patients in Study 4040 were weighed by their estimated odds of enrolment in Trial NEURTRINO as opposed to enrolment in Study 4040 in an attempt to balance baseline characteristics between trial subjects when comparing the treatment effect of DCV+SOF vs SOF+PR. This analysis could not be verified during the evaluation.

Source: Table 11, Attachment C to the submission

- 6.15 An unadjusted single arm comparison of DCV+SOF versus TVR+PR, based on non-cirrhotic patients in the telaprevir ADVANCE trial, was conducted during the evaluation. It should be noted that, due to exchangeability issues between studies, the results of these unadjusted indirect comparisons were highly imprecise.

Indirect comparison of SVR24 for DCV+SOF and TVR+PR in non-cirrhotic treatment-naïve genotype 1 patients

	DCV+SOF <sup>a</sup> n/N % (95%CI)	TVR+PR <sup>b</sup> n/N % (95%CI)	Absolute difference (95% CI)
Genotype 1 non-cirrhotic patients	39/41 95.1% (83.5%, 99.4%)	270/342 78.9% (74.2%, 83.1%)	16.2% (8.3%, 24.1%)

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

<sup>a</sup> Group G, treatment-naïve genotype 1 patients treated with DCV12+SOF12

<sup>b</sup> SVR24 for non-cirrhotic treatment-naïve genotype 1 patients in the ADVANCE trial, as reported in the PI for telaprevir

## Comparative harms

- 6.16 The safety data from Study 4040 are presented in the table below.

Summary of key on-treatment adverse events in Study 4040

Study 4040	Proposed drug n with event/N (%)
Treatment related AEs	130/211 (61.6%)
Serious AEs <sup>a</sup>	15/211 (7.1%)
Grade 3/4 AEs	7/211 (3.3%)
Number discontinued	2 /211 (0.9%)
Number died	0

AE = adverse event

<sup>a</sup> 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; Table S.6.6.3, p622 Study 4040 clinical study report

- 6.17 No serious adverse events that were considered to be specifically related to daclatasvir were observed in the study apart from four cases of overdose which did not result in treatment intervention or clinical symptoms. The most common on-treatment adverse events in Study 4040 were fatigue (37.0%), headache (28.9%), nausea (19.4%), arthralgia (10.0%) and diarrhoea (10.0%). Anaemia was only reported in patients receiving concomitant ribavirin. Two patients discontinued therapy due to adverse events: one had a cerebrovascular accident (Grade 2) at week 22, and one had an AE of fibromyalgia (Grade 3) at week 10. Both events were considered by the investigator not to be related to study drug.
- 6.18 There were insufficient data to reliably determine the safety profile of DCV+SOF, especially in terms of uncommon or rare treatment-related adverse events.

**Benefits/harms**

- 6.19 A summary of the comparative benefits and harms for DCV + SOF versus 'no treatment' is presented in the table below, based on the evidence provided in the submission and in the PSCR.

Summary of comparative benefits and harms for DCV + SOF ± R relative to No treatment

Patient group	Comparison	Benefits (SVR12)*	Harm**
Genotype 1, treatment-naïve Non-cirrhotic	for every 100 patients treated with <u>DCV12+SO12</u> in comparison to <u>no treatment</u>	<ul style="list-style-type: none"> <li>Approximately 100 additional patients would be expected to achieve an SVR</li> </ul>	<ul style="list-style-type: none"> <li>Approximately 7 additional patients would experience a serious AE</li> <li>Approximately 2 additional patients would experience a Grade 3/4 AE</li> </ul>
Genotype 2/3, treatment-naïve Non-cirrhotic	for every 100 patients treated with <u>DCV24 + SO12</u> in comparison to <u>no treatment</u>	<ul style="list-style-type: none"> <li>Approximately 93 additional patients would be expected to achieve an SVR</li> </ul>	
Genotype 3, treatment-naïve Non-cirrhotic	for every 100 patients treated with <u>DCV12 + SO12</u> in comparison to <u>no treatment</u>	<ul style="list-style-type: none"> <li>Approximately 97 additional patients would be expected to achieve an SVR ^</li> </ul>	
Genotype 3, treatment-naïve Cirrhotic	for every 100 patients treated with <u>DCV12 + SO12</u> in comparison to <u>no treatment</u>	<ul style="list-style-type: none"> <li>Approximately 58 additional patients would be expected to achieve an SVR ^</li> </ul>	
Genotype 1, treatment-experienced Non-cirrhotic	for every 100 patients treated with <u>DCV24 + SO12</u> in comparison to <u>no treatment</u> :	<ul style="list-style-type: none"> <li>Approximately 100 additional patients would be expected to achieve an SVR</li> </ul>	
Genotype 3, treatment-experienced Non-cirrhotic	for every 100 patients treated with <u>DCV12 + SO12</u> in comparison to <u>no treatment</u>	<ul style="list-style-type: none"> <li>Approximately 94 additional patients would be expected to achieve an SVR ^</li> </ul>	
Genotype 3, treatment-experienced Cirrhotic	for every 100 patients treated with <u>DCV12 + SO12</u> in comparison to <u>no treatment</u>	<ul style="list-style-type: none"> <li>Approximately 69 additional patients would be expected to achieve an SVR ^</li> </ul>	

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

\*\* Based on on-treatment adverse events

^ Sourced from Nelson, D.R. et al. Hepatology (2015). Accepted online ahead of print: <http://onlinelibrary.wiley.com/doi/10.1002/hep.27726/pdf>.

DCV = daclatasvir; SOF = sofosbuvir; R = ribavirin; AE = adverse event

Source: Compiled during the evaluation and preparation of the ESC ADV

## Clinical claim

- 6.20 The submission described DCV+SOF as superior in terms of both comparative effectiveness and comparative safety over TVR+PR in patients with genotype 1 HCV, and superior in terms of both effectiveness and safety to PR in patients with genotypes 2 and 3 HCV. This claim was only relevant to the minority of patients seeking treatment with interferon-based treatments rather than waiting for the all-oral, interferon-free regimens to become available. Although the results of the matching-adjusted indirect comparison relative to TVR+PR indicated that DCV+SOF had superior SVR rates, this benefit was likely over-estimated due to the inclusion of cirrhotic patients in the comparator arm but not the intervention arm. With regard to the 'qualitative' comparisons and the unadjusted comparisons against the active comparators, exchangeability concerns precluded any confidence in the estimate of the magnitude of the differences in the treatment effect. The claim of superiority in terms of comparative safety is reasonable, given that no AEs specifically related to daclatasvir were identified in Study 4040, while the adverse events associated with PR therapy are considerable.
- 6.21 With regard to the comparator considered appropriate by the PBAC, DCV+SOF was superior to 'no treatment' in terms of therapeutic effectiveness and inferior in terms of safety in both treatment-naïve and treatment-experienced patients of all genotypes.
- 6.22 Based on the evidence provided in the submission, the following issues remained unresolved:
- Whether the proposed treatment duration of 12 weeks in all genotypes was appropriate, regardless of treatment history or cirrhosis status, given that there were no data supporting this regimen in any patient subgroup other than non-cirrhotic treatment-naïve patients with genotype 1 HCV infection;
  - There was no evidence provided on DCV+SOF treatment, of any duration, in the following patients:
    - Treatment-experienced patients with genotype 2,3, 4, 5 and 6 HCV;
    - Patients with documented cirrhosis ;
    - Treatment-naïve patients with genotype 4, 5 and 6 HCV; and
    - Patients with HCV and HIV or HBV co-infection.
- 6.23 The ESC noted that results from ALLY-3 open label trial of DCV+SOF12 for GT3 patients became available after submission. While the study confirmed high rates of SVR with DCV+SOF12 for GT3 naïve and experienced patients without cirrhosis, observed SVR was lower among the small number of naïve and experienced patients with cirrhosis.
- 6.24 The PBAC considered that the claim of superior comparative effectiveness and inferior comparative safety to no treatment was reasonable for GT1 naïve non-cirrhotic patients and for GT3 naïve/experienced cirrhotic/non-cirrhotic patients.
- 6.25 Based on the evidence provided in the submission, the PBAC considered that the clinical efficacy of 12 weeks of treatment with daclatasvir in combination with sofosbuvir was not supported in the following groups: treatment experienced Genotype 1 CHC patients, treatment naïve cirrhotic Genotype 1 CHC patients,

Genotype 2 CHC patients, Genotype 4 CHC patients, Genotype 5 CHC patients and Genotype 6 CHC patients.

- 6.26 The PBAC noted the SVR12 reported in publications of HCV treatment with sofosbuvir in combination with ribarivin (SOF+R) and ledipasvir/sofosbuvir (LDV/SOF). Though based on unadjusted comparison of SVR results, the PBAC considered that it was reasonable to accept that DCV12 +SOF12 was non-inferior for comparative efficacy with
- LDV/SOF in treatment naive non-cirrhotic Genotype 1 patients.
  - SOF24 +R24 in treatment naive non-cirrhotic Genotype 3 patients.
- 6.27 Based on the available data, the Committee considered that it was reasonable to consider that the combination of DCV + SOF had a similar safety profile as LDV/SOF in treatment naive non-cirrhotic Genotype 1 patients and SOF24 +R24 in treatment naive non-cirrhotic Genotype 3 patients.

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

### **Economic analysis**

- 6.28 Results of the economic evaluation of DCV+SOF presented in the section below were based on the sofosbuvir price assumed by the submission (DPMQ: \$ [REDACTED] for 12-week treatment), not the sofosbuvir price proposed by the sofosbuvir sponsor.
- 6.29 The submission presented a modelled economic evaluation based on an unadjusted comparison of SVR results from single arms of different studies.
- 6.30 The structure consisted of a Markov state-transition model, with 16 health states that described the progression of disease over a lifetime. Patients with chronic genotypes 1-4 HCV infection entered the model at 51 years of age and were stratified by various fibrosis stages (F0-F4). Patients would receive HCV therapy or no treatment. Treatment effects were incorporated into the model in the form of SVR rates relevant to the specific HCV therapies. After HCV treatment, a proportion of patients transitioned from chronic HCV infection disease states (ie F0 to F4) to the corresponding SVR health state. Once in the SVR states, the patient remained there until death, but with small risks of re-infection (ie relapsing back into chronic HCV health states) or transition from compensated cirrhotic disease with SVR to a hepatocellular carcinoma health state. If patients did not achieve an SVR, they remained in their current health states or progressed to more severe health states through various fibrosis stages in a sequential order (F0 to F4) and, subsequently, to complications. These complications included decompensated cirrhosis, hepatocellular carcinoma, liver transplant and disease-related mortality.

#### **Summary of model structure and rationale**

Time horizon	Lifetime (cycles until cohort reaches 100 years of age – 49 years in the base case). This was longer than the PBAC's recommendation of a 30 year time horizon (7.10, Item 5.17 PSD, July 2014 PBAC).
Outcomes	QALYs
Methods used to generate results	Cohort expected value analysis
Cycle length	1 year

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Transition probabilities	Based on literature review.
Discount rate	5% for costs and outcomes
Software package	Excel 2010

PSD = public summary document; QALY = quality-adjusted life year; SVR = sustained virologic response.  
Source: compiled during the evaluation

- 6.31 The model assumed that 100% of patients were treatment-naïve. Although this is most consistent with the trial data, the modelled population was not representative of the population for whom the PBS listing was sought.
- 6.32 No data on SVR rates were available for cirrhotic patients as Study 4040 excluded patients with documented cirrhosis. The assumption that the SVR rates were the same in non-cirrhotic and cirrhotic patients would have biased the results in favour of DCV+SOF when applied to the whole treatment-naïve HCV population. The ESC noted the PSCR (p4) that the ICER might be lower in a population including cirrhotic patients, despite lower SVR rates, because of the greater risk of HCV complications. Nonetheless, the ESC considered the reduced and imprecise SVR rates observed among cirrhotic patients with DCV+SOF12 remained a source of uncertainty in the economic analysis. Alternatively, if all patients were assumed to have non-cirrhotic disease (with the relative proportions of patients with F0-F3 disease remaining the same as the base case), the ESC noted that ICER for GT1 rose from the \$15,000/QALY - \$45,000/QALY to \$15,000/QALY - \$45,000/QALY.
- 6.33 A summary of the key drivers of the model is presented in the table below.

Key drivers of the DCV+SOF model

Description	Method/Value	Impact
Treatment duration of DCV+SOF therapy for genotype 2/3 HCV	12 weeks. The submission assumed that the treatment effect from a 12-week treatment would be equivalent to a 24-week DCV+SOF treatment as observed from Study 4040. This was not justified in the submission.	High, favours DCV+SOF
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+SOF
SVR rate associated with DCV+SOF in the proposed PBS population	95.1% for genotype 1/4 and 93.3% for genotype 2/3. SVR rates were sourced from results of relevant genotype subgroups in Study 4040, where treatment-experienced patients and patients with documented cirrhotic disease were not represented.	Moderate, favours DCV+SOF
Time horizon	49 years. This was longer than the PBAC advice of a 30 year time horizon for economic models in other HCV submissions (Sofosbuvir draft PSD, July 2014 PBAC meeting)	Moderate, favours DCV+SOF
Transition probabilities	The model applied the transition probabilities used in the BCG report (2012). Many transition probabilities used in the	Moderate, favours DCV+SOF

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Description	Method/Value	Impact
	BCG model were derived from older longitudinal studies. The PBAC considered that the data from old studies to estimate transition probabilities was likely to overestimate the likelihood of progression compared to present rates (Telaprevir PSD March 2012 PBAC meeting)	

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

Source: compiled during the evaluation

- 6.34 The submission presented an economic model of DCV+SOF compared with a mixture of active treatment and no treatment (67% of patients were assumed to be treated with TVR12+PR24/48 for genotype 1, PR24 for genotype 2/3, and PR48 for genotype 4 HCV; and the remaining 33% receiving no treatment). The ESC noted that in the context of the growing preference for IFN-free therapy, the most relevant comparator was no treatment.
- 6.35 The results of economic evaluation of DCV+SOF compared to no treatment and compared to current HCV therapies (TVR+PR for genotype 1 and PR for genotypes 2-4) are summarised in the tables below. The cost of sofosbuvir was assumed by this submission and not as proposed by the sponsor of sofosbuvir.

Results of the DCV+SOF economic evaluation (genotype 1 HCV)

	DCV12+SOF12	No treatment	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs <sup>a</sup>	11.643	9.883	1.760
Incremental cost/extra QALY gained			\$ [REDACTED]
	DCV12+SOF12	TVR12+PR24/48 <sup>b</sup>	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs <sup>a</sup>	11.643	11.343	0.300
Incremental cost/extra QALY gained			\$ [REDACTED]

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

<sup>a</sup> Using a utility value of 0.60 for the F4(SVR) health state. The submission assumed identical utility values (0.720) for patients achieving SVR from moderate disease (F2/F3 (SVR)) and those achieving SVR from compensated cirrhosis (F4(SVR)). This was unreasonable. Based on the submission's assumption of a utility gain of 0.05 in patients achieving SVR, the utility for F4(SVR) health state should be 0.60 (= 0.55 (utility value for F4) + 0.05).

<sup>b</sup> Assuming an SVR rate of 78.9% (SVR rate in non-cirrhotic treatment-naïve patients in ADVANCE trial) for patients treated with TVR+PR

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

Results of the DCV+SOF economic evaluation (genotypes 2 and 3 HCV)

	DCV12+SOF12	No treatment	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs <sup>a</sup>	11.610	9.883	1.727
Incremental cost/extra QALY gained			\$ [REDACTED]
	DCV12+SOF12	PR24	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs <sup>a</sup>	11.610	11.139	0.471
Incremental cost/extra QALY gained			\$ [REDACTED]

DCV = daclatasvir; HCV = hepatitis C virus; PR = peginterferon and ribavirin; QALY = quality-adjusted life year; SOF = sofosbuvir

<sup>a</sup> Using a utility value of 0.60 for the F4(SVR) health state.  
 Source: Compiled during the evaluation from "DCV Economic Evaluation.xlsx" workbook

**Results of the DCV+SOF economic evaluation (genotype 4 HCV)**

	DCV12+SOF12	No treatment	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs <sup>a</sup>	11.643	9.883	1.760
<b>Incremental cost/extra QALY gained</b>			<b>\$ [REDACTED]</b>
	DCV12+SOF12	PR48	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs <sup>a</sup>	11.643	10.834	0.809
<b>Incremental cost/extra QALY gained</b>			<b>\$ [REDACTED]</b>

DCV = daclatasvir; HCV = hepatitis C virus; PR = peginterferon and ribavirin; QALY = quality-adjusted life year; SOF = sofosbuvir.

<sup>a</sup> Using a utility value of 0.60 for the F4(SVR) health state.  
 Source: Compiled during the evaluation from "DCV Economic Evaluation.xlsx" workbook

6.36 In addition to the cost of sofosbuvir in this submission not being the sofosbuvir proposed price, the following concerns were noted:

- The SVR rates associated with DCV+SOF in the model were likely overestimated (as patients with poor treatment response, eg cirrhotic patients, were excluded from Study 4040);
- Unadjusted single arm indirect comparisons with the active treatment comparator arms
- 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, p4).

6.37 The SVR rate used in the model for genotype 2/3 HCV (93.3%) was taken from Study 4040, where patients infected with genotype 2/3 HCV were treated with 24 weeks of DCV+SOF. The submission's assumption that 12-weeks of DCV+SOF was as effective as a 24-week treatment with DCV+SOF in genotype 2/3 patients was not justified. If the costs for 24 weeks of DCV+SOF were used in the model, the ICER would have been \$45,000/QALY - \$75,000/QALY, corresponding to a QALY gain of 1.727 at an additional cost of \$75,000/QALY - \$105,000/QALY. The ESC noted that results from ALLY-3 open label trial of DCV+SOF12 became available after submission, supporting a claim of high SVR for GT3 without cirrhosis, but more modest SVR in GT3 patients with cirrhosis.

- 6.38 During the evaluation, additional sensitivity analyses were conducted for DCV+SOF versus no treatment in genotype 1 patients. The results indicated that the model was very sensitive to the assumption of a utility gain in patients achieving SVR versus those not achieving SVR. The model was moderately sensitive in univariate analyses to the SVR rate associated with DCV+SOF treatment, time horizon and transition probabilities. If the model used a time horizon of 30 years, the NICE transition probabilities and nil utility gain due to achieving an SVR, the ICER tripled, increasing to \$45,000/QALY - \$75,000/QALY from a base case of \$15,000/QALY - \$45,000/QALY.

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

Variables	Assumptions	Incremental costs	Incremental QALYs	ICERs
Base case				
		\$ [REDACTED]	1.760	\$ [REDACTED]
Univariate sensitivity analyses				
SVR rate associated with DCV+SOF (95.1%)	Upper 95% CI rate (99.4%)	\$ [REDACTED]	1.839	\$ [REDACTED]
	Lower 95% CI of SVR rate (83.5%)	\$ [REDACTED]	1.545	\$ [REDACTED]
Time horizon (base case: 49 years)	30 years (PBAC recommendation)	\$ [REDACTED]	1.534	\$ [REDACTED]
Transition probabilities	Using inputs from the NICE model <sup>4a</sup>	\$ [REDACTED]	1.456	\$ [REDACTED]
Utilities (base case: sourced from Wright et al 2006)	Using Townsend utility values	\$ [REDACTED]	1.228	\$ [REDACTED]
	Using Townsend utility values, but assuming a 0.05 utility gain due to achieving SVR	\$ [REDACTED]	1.628	\$ [REDACTED]
	Using Wright utility values, but assuming no utility increment due to achieving SVR	\$ [REDACTED]	1.100	\$ [REDACTED]
Multivariate sensitivity analyses				
Time horizon + Transition probabilities	30 years Using inputs from the NICE model <sup>a</sup>	\$ [REDACTED]	1.280	\$ [REDACTED]
Time horizon + Transition probabilities + Utilities	30 years Using inputs from the NICE model <sup>a</sup> Using Townsend utility values	\$ [REDACTED]	0.813	\$ [REDACTED]
Time horizon + Transition probabilities + Utilities	30 years Using inputs from the NICE model <sup>a</sup> Assuming no utilities increment due to SVR	\$ [REDACTED]	0.648	\$ [REDACTED]

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

<sup>a</sup> Using the transition probabilities as presented in Table D(I).4.3 of 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 a utility value of 0.60 for the F4(SVR) health state.

- 6.39 The ESC noted the sensitivity analysis for GT1 patients presented in the PSCR (p4, presented below) resulting in an ICER of \$15,000/QALY - \$45,000/QALY.

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Revisions to base case estimates for DCV + SOF vs. no treatment in a HCV GT1 population (PSCR)

Variable tested	Value	Incremental cost	Incremental QALY	ICER
Base case (submission) vs. no treatment		\$ [REDACTED]	1.8888	\$ [REDACTED]
Correcting utility value for F4(SVR)	0.72 to 0.60	\$ [REDACTED]	1.7602	\$ [REDACTED]
Reduced utility increment associated with SVR as per NICE assessment	0.05 to 0.041	\$ [REDACTED]	1.6175	\$ [REDACTED]
Reduce model duration to 30 years	49 to 30 years	\$ [REDACTED]	1.3982	\$ [REDACTED]
Sensitivity analysis incorporating evaluator's suggested changes		\$ [REDACTED]	1.3982	\$ [REDACTED]

- 6.40 The ESC applied the same assumptions to GT1 and GT3 patients, based on study 4040 and ALLY3 data. The ESC noted that the ICER was not sensitive to the genotype or the source of the clinical evidence.

Revisions to base case estimates for DCV + SOF vs. no treatment in a HCV GT1 and GT3 population

	ICER
GT1 treatment naïve	(study 4040 from submission) 100% Non-cirrhotic: \$ [REDACTED] 100% cirrhotic: \$ [REDACTED] 91% non-cirrhotic & 9% cirrhotic (as in submission): \$ [REDACTED]
GT1 treatment experienced	(study 4040 from submission) Not considered in the submission
GT3 treatment naïve	(study 4040 from submission) 100% Non-cirrhotic: \$ [REDACTED] 100% cirrhotic: \$ [REDACTED] <sup>a</sup> 91% non-cirrhotic & 9% cirrhotic (as in submission): \$ [REDACTED]  (ALLY 3 provided in PSCR) 100% Non-cirrhotic: \$ [REDACTED] 100% cirrhotic: \$ [REDACTED] 91% non-cirrhotic & 9% cirrhotic(as in submission): \$ [REDACTED]
GT3 treatment experienced	(study 4040 from submission) Not considered in the submission  (ALLY 3 provided in PSCR) 100% Non-cirrhotic: \$ [REDACTED] 100% cirrhotic: \$ [REDACTED] 91% non-cirrhotic & 9% cirrhotic(as in submission): \$ [REDACTED]

<sup>a</sup> submission assumed a similar SVR rate for cirrhotic patients to those without liver cirrhosis.

6.41 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 as 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 regimens were cirrhotic. ([http://www.natap.org/2014/AASLDEASL/AASLDEASL\\_01.htm](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.
- 6.42 The PBAC noted in the pre-PBAC response that the sponsor sought clinical advice that confirmed that patients with more advanced fibrosis would be treated ahead of those with less fibrosis.
- 6.43 The PBAC noted the cost-effective analysis presented in the submission. The PBAC agreed with the revised base case presented in the ESC Advice. The PBAC disagreed with the sponsor and considered that a 30 year time horizon was appropriate. Multivariate sensitivity analysis adjusting the time horizon, transition probabilities, and utilities produced ICERs outside the range of \$15,000 to \$45,000/QALY. The PBAC noted that the incremental cost-effectiveness ratio when the proposed price of the SOF was imputed into the model, was outside the range of \$15,000 to \$45,000/QALY
- 6.44 The PBAC also noted that ICER might 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.
- 6.45 Overall, the economic model presented in the submission favoured 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.
- 6.46 Though all the data presented to the committee was based on unadjusted single arms of studies, the PBAC considered that it was reasonable to assume that one treatment course of DCV+SOF 12 weeks was as effective as one course of LDV/SOF for genotype 1 patients and SOF24+R24 in genotype 3 patients. The PBAC considered that there was no basis on which to recommend that DCV+SOF be more expensive than LDV/SOF for genotype 1 patients and SOF24+R24 in genotype 3 patients
- 6.47 Though the PBAC did not accept all aspects of the economic model as submitted, to examine the comparative price setting, the model parameters were modified in the following way.
- For GT1a as representative of the cost of treating Genotype 1 patients: The model parameters were adjusted in 'DCV HCV Economic\_Model\_Nov14.xlsm' to achieve

the following difference in cost of \$15,000 - \$45,000 and difference in QALY of 1.8888, in the 'Results' tab, with Control Arm Cost set to \$0. In 'ModellInputs', the following inputs were applied: (1) the comparator regimen and "Second line" treatment (both arms) was set to no treatment and the treatment regimen was set to 'DCV+SOF'; (2) Genotype was set to 'GT1a'; (3) a regimen cost was entered into 'Sent to the model' cell (E64) to achieve the incremental cost and QALY values specified above.

- For GT3: The model parameters were adjusted in 'DCV HCV Economic\_Model\_Nov14.xlsm' to achieve the following difference in cost of \$15,000 - \$45,000 and difference in QALY of 1.8532, in the 'Results' tab, with Control Arm Cost set to \$0. In 'ModellInputs', the following inputs were applied: (1) the comparator regimen and "Second line" treatment (both arms) was set to no treatment and the treatment regimen was set to 'DCV+SOF'; (2) Genotype was set to 'GT3'; (3) a regimen cost was entered into 'Sent to the model' cell (E64) to achieve the incremental cost and QALY values specified above.

6.48 The PBAC noted that the draft product information included:

- Consider adding ribavirin to the DAKLINZA/sofosbuvir 12-week regimen or prolonging treatment duration to 24 weeks for patients with cirrhosis or with other negative prognostic factors such as prior treatment experience (eg, protease inhibitor, peginterferon alfa and ribavirin).
- The dose of DAKLINZA should be reduced to 30 mg once daily when coadministered with strong inhibitors of CYP3A4 (using the 30 mg tablet; DAKLINZA tablets should not be broken).
- The dose of DAKLINZA should be increased to 90 mg once daily (three 30 mg tablets or one 60 mg and one 30 mg tablet) when coadministered with moderate inducers of CYP3A4.

6.49 The PBAC recommended that the cost to achieve a SVR12 should be independent of the treatment duration (such as 12 week or 24 weeks) and treatment dose (30 mg, 60mg and 90mg) considered to be appropriate to achieve a SVR in patients.

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

6.50 Cost of daclatasvir: \$ [REDACTED] for a 12 week course.

Cost of sofosbuvir: \$ [REDACTED] for a 12 week course.

The cost of DCV+SOF is based on the submission's assumption that the maximum quantity for sofosbuvir is sufficient for a 12 week course and that the dispensed price for maximum quantity (DPMQ) is \$ [REDACTED]. Patients only receive one 12 week course of treatment.

### **Estimated PBS usage & financial implications**

6.51 The submission was considered by the Drug Utilisation Sub-Committee (DUSC).

6.52 The following estimates of PBS usage and financial implications were presented in the submission. At year 5, the estimated number of patients was 10,000 – 50,000 and the net cost to the PBS would be more than \$100 million.

Estimated net financial cost/year to the PBS/RPBS

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Total cost DCV+SOF</b>					
Patients treated					
Total cost	\$	\$	\$	\$	\$
Total cost <sup>a</sup>	\$	\$	\$	\$	\$
Patients co-payments	\$	\$	\$	\$	\$
Cost to PBS/RPBS	\$	\$	\$	\$	\$
Cost to PBS/RPBS <sup>a</sup>	\$	\$	\$	\$	\$
<b>Cost off-sets form current treatment regimens</b>					
Patients treated					
Total cost	\$	\$	\$	\$	\$
Patient co-payments	\$	\$	\$	\$	\$
Savings to PBS/RPBS	\$	\$	\$	\$	\$
Additional patients treated					
Net total cost	\$	\$	\$	\$	\$
Net total cost <sup>a</sup>	\$	\$	\$	\$	\$
Net patients co-payments	\$	\$	\$	\$	\$
Net cost to the PBS/RPBS	\$	\$	\$	\$	\$
Net cost to the PBS/RPBS <sup>a</sup>	\$	\$	\$	\$	\$

DCV = daclatasvir; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; SOF = sofosbuvir

<sup>a</sup> Based on DPMQ for daclatasvir and weighted cost for sofosbuvir (87% public (ex-manufacturer cost) and 13% private (DPMQ))

Source: Commentary on the Main Submission, Table E(l).4.2.p113.

6.53 DUSC considered that the estimates of patients treated presented in the submission were reasonable. However, the treatment rate once all-oral interferon-free treatment regimens become available is unknown as:

- There is a large pool of people living with CHC infection(230,000);
- The number of patients who are deferring treatment to receive interferon-free therapy is unknown; and
- It is uncertain whether and when the current model of care involving specialist treatment centres will change to a greater involvement of primary care in HCV prescribing with a subsequent broader access to treatment.

6.54 DUSC considered that the financial estimates were highly uncertain and likely to be underestimated as:

- The cost of sofosbuvir is unknown and an assumed price is used by the submission.
- It would be at the discretion of the prescriber whether patients with genotype 1, 2, or 3 HCV would receive the recommended 12 weeks of treatment or the maximum 24 weeks of DCV+SOF which is allowed under the requested restriction.
- The projected offsets for substituted HCV treatment are significantly greater

than the current PBS expenditure on HCV medicines. The submission’s assumption of a growth in the use of currently available medicines is unlikely given that patients are deferring treatment with interferon-containing therapy.

- 6.55 Taking account of the proposed drug prices, treatment targets in the Fourth National Hepatitis C Strategy and assuming that care continues to be delivered through specialist treatment centres, DUSC estimated the following number of patients of all genotypes would be treated over the first five years of listing at a net cost to the PBS/RPBS of approximately \$3 billion over five years.

Year 1	Year 2	Year 3	Year 4	Year 5
█	█	█	█	█

- 6.56 The PBAC noted the DUSC advice on the item. The PBAC was of the view that the DUSC estimates for patients likely to be treated were appropriate. At year 1, the estimated number of patients with any HCV genotype was 6,660 and the net cost to the PBS would be approximately more than \$100 million, if based on the cost per treatment considered appropriate by the PBAC. At year 5, the estimated number of patients was 15,000 and the net cost to the PBS would be approximately more than \$100 million. Over 5 years, it is estimated that approximately 61 500 patients would be treated, and the net cost would be more than \$100 million. The PBAC noted that currently approximately \$87.5 million is spent on treatments for CHC, while, if the health system had the capacity, to treat all CHC patients over 5 years, the cost would be over more than \$100 million.

### Financial Management – Risk Sharing Arrangements

- 6.57 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 \$█, with a rebate applied to the proportion of daclatasvir dispensed for use in combination with asunaprevir to reduce the effective DPMQ to \$█. The DPMQ of daclatasvir for the proportion dispensed for use in combination with sofosbuvir would remain at \$█, with no rebate applied. If only daclatasvir when combined with asunaprevir is listed, the proposed DPMQ of daclatasvir was \$█, with no rebate.
- 6.58 The PBAC noted the estimates of patients being treated presented in the DUSC advice, based on treatment targets in the Fourth National Hepatitis C Strategy 2014-2017 and assuming that care continues to be delivered through specialist treatment centres. The PBAC noted initiatives to support a greater role of primary care in the prescribing. Though the magnitude of this uptake is unknown, the PBAC considered that it was reasonable to assume that the estimates from DUSC over the next 5 years would remain appropriate in the context of a General Schedule listing, given that treatment would initially continue in specialist treatment centres; and that the uptake by general practitioners to become accredited to manage HCV may be low as noted in the NSW Hepatitis C Strategy 2014-2020. The PBAC recommended a Risk Share Arrangement (RSA).
- 6.59 The PBAC recommended that the RSA should consist of a cap on expenditure, with a 100% rebate for budget certainty. The cap on expenditure should be based on the

DUSC estimates. The PBAC considered that the advice received from the Australian Liver Association, namely Bruggmann et al. (2014), was the most appropriate the source of HCV genotype distribution in Australia. The Committee recommended that the Department negotiate RSAs based on DUSC estimates of the patient population and treatment course per patient for each medicine, in a manner that can be implemented and managed by the Department. The PBAC emphasised the importance of ensuring that these arrangements can be implemented in a way that would manage the overall cost to the Commonwealth for these medicines. Currently, the sponsor of DCV, and other sponsors of HCV treatments used in combination with SOF would be part of such agreement.

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the Authority Required listing of daclatasivir in combination with sofosbuvir for the treatment of Genotype 1 chronic hepatitis C (CHC) in treatment naïve non-cirrhotic patients. Listing was recommended on the basis of acceptable cost effectiveness over no treatment, however the PBAC recommended that the price of a course of treatment should be the same as the price of a course of treatment with ledipasvir/sofosbuvir.
- 7.2 The PBAC recommended the Authority Required listing of daclatasivir in combination with sofosbuvir for the treatment of Genotype 3 chronic hepatitis C (CHC). Listing was recommended on the basis of acceptable cost effectiveness over no treatment, however the PBAC recommended that the price of a course of treatment should be the same as the price of a course of treatment with sofosbuvir in combination with ribavirin (24 weeks).
- 7.3 The PBAC considered that there was no basis on which to make a cost effectiveness recommendation for daclatasivir in combination with sofosbuvir over ledipasvir/sofosbuvir (Genotype 1) or sofosbuvir in combination with ribavirin (Genotype 3).
- 7.4 Based on the evidence provided in the submission, the PBAC considered that the clinical efficacy of 12 weeks of treatment with daclatasivir in combination with sofosbuvir was not supported in the following groups: treatment experienced Genotype 1 CHC patients, treatment naïve cirrhotic Genotype 1 CHC patients, Genotype 2 CHC patients, Genotype 4 CHC patients, Genotype 5 CHC patients and Genotype 6 CHC patients.
- 7.5 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.
- 7.6 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. The PBAC considered that that the Department, in consultation with clinical experts, should explore whether prescribing should be available to practitioners who have gained accreditation (as occurs currently for Section 100 prescribing) or in a Share Care Model (namely, in consultation with a clinician with experience of prescribing treatment for CHC, such as a hepatologist or infectious disease physician). The PBAC considered that an Authority Required listing was appropriate, but whether this Authority is written, telephone or streamlined remains to be finalised. The conditions of the listing would also depend on the final registered Product Information.

- 7.7 The submissions 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 and that the listing of DCV could only progress if sofosbuvir is available on the PBS.
- 7.8 The PBAC considered that the comparative magnitude of the benefit (SVR12) of the treatment presented in the submission was uncertain due to the reliance on single arms of trials, some of which involved small number of patients. The PBAC was of the view that the evidence provided in the submission was the best available as the development programs of DAA has been based predominately on uncontrolled trials.
- 7.9 The PBAC noted the SVR12 reported in publications of HCV treatment with sofosbuvir in combination with ribarivin and ledipasvir/sofosbuvir (LDV/SOF). The PBAC considered that it was reasonable to accept that DCV12 +SOF12 was non-inferior for comparative efficacy with
- LDV/SOF in treatment naive non-cirrhotic Genotype 1 patients.
  - SOF24 +R24 in treatment naive non-cirrhotic Genotype 3 patients.
- 7.10 Based on the available data, the Committee considered that it was reasonable to consider that the combination of DCV + SOF had a similar safety profile as LDV/SOF in treatment naive non-cirrhotic Genotype 1 patients and SOF24 +R24 in treatment naive non-cirrhotic Genotype 3 patients.
- 7.11 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 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.

- 7.12 The PBAC noted the DUSC advice on the item. The PBAC was of the view that the DUSC estimates for patients likely to be treated were appropriate. At year 1, the estimated number of patients was 6,660 and the net cost to the PBS would be approximately more than \$100 million, if based on the cost per treatment considered appropriate by the PBAC. At year 5, the estimated number of patients was 15,000 and the net cost to the PBS would be approximately more than \$100 million. Over 5 year, it is estimated that approximately 61 500 patients would be treated, and the net cost would be more than \$100 million.
- 7.13 The PBAC considered that it would be appropriate for sponsors of combinations containing all oral agents targeted against HCV proteins to split the price of a treatment course equally.
- 7.14 In accordance with subsection 101(3BA) of the National Health Act 1953, the PBAC advised that the Committee is of the opinion that, on the basis of the material available at the March 2015 meeting, daclatasvir should not be treated as interchangeable with other recommended treatments of CHC on an individual patient basis.
- 7.15 The PBAC noted that suitability of prescribing daclatasvir by nurse practitioners would depend on the final listing conditions of daclatasvir. The PBAC were of a mind that in principle nurse practitioners prescribing was likely to be suitable in the context of a share care model.
- 7.16 The PBAC recommended that the Safety Net 20 Day Rule should not apply.
- 7.17 The resubmission is not eligible for an Independent Review, because the PBAC made a positive recommendation.
- 7.18 The PBAC acknowledged that there was a high clinical need for more effective and tolerable treatment for HCV. The PBAC noted that there is a large number (around 230,000) of patients with the chronic HCV who are untreated and that the utilisation of existing listings was low as patients were contraindicated or unwilling to take interferon. Based on the prevalence of HCV and the financial estimate presented in the submission, the PBAC considered that there would be a significant opportunity cost to the Commonwealth of listing oral treatments as their uptake would be substantially higher than currently subsidised medicines. The PBAC reiterated its view that the clinical management of individuals with HCV is moving so rapidly that a broader Government and community approach is needed to maximise the clinical outcomes and patient access to treatment. As well as subsidising new treatment on the PBS, other factors that increase the capacity to treat patients need to be explored.
- 7.19 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:**

Recommended

**8 Recommended listing**

- 8.1 Add new item:  
Restriction to be finalised

**9 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.

**10 Sponsor's Comment**

The Sponsor had no comment.