7.02 DACLATASVIR, tablet, 60mg or 30mg, Daklinza®, Bristol-Myers Squibb.

1 Purpose of Application

1.1 In March 2015, the PBAC recommended a general schedule Authority Required PBS listing for daclatasvir (DCV) in combination with sofosbuvir (SOF) for the treatment of genotype 1 chronic hepatitis C (CHC) infection in treatment naïve non-cirrhotic patients, and for the treatment of genotype 3 CHC infection. The current re-submission sought an extension of the recommended PBS listings to include all CHC genotypes, irrespective of previous treatment history or cirrhosis status. The March 2015 submission was the only previous submission considered by PBAC.

2 Requested listing

2.1 The requested listing from March 2015 is reproduced below:

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	60mg tablet Patient must have compensated liver disease, The treatment must be limited to a maximum duration of 24 weeks[a], 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 30mg tablet 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
Population criteria	Patient must be 18 years or older

2.2 The re-submission was seeking extension of the recommended listing to include the following patient groups:

- Genotype 1 hepatitis C virus (HCV) treatment naïve patients with cirrhosis,
- Genotype 1 HCV treatment experienced patients, irrespective of cirrhosis status,
- Genotypes 2, 4, 5 and 6 HCV patients, irrespective of previous treatment history or cirrhosis status.

2.3 There was some uncertainty regarding the proposed dose regimen for DCV+SOF in the patient subgroups for which extension of the approved listing was requested, as this was not specified in the re-submission. It was assumed that this remained unchanged from the original submission, in which the proposed dose regimen for all genotypes, irrespective of previous treatment history or cirrhotic status, was daclatasvir 60mg once daily, in combination with SOF 400mg once daily with food,

for 12 weeks, without ribavirin (RBV). This regimen was not consistent with the treatment recommendations in the TGA-approved Product Information (PI) or with current treatment guidelines, in which the recommended regimen varied between patient subgroups in respect to treatment duration and concomitant use of ribavirin, dependent on HCV genotype, previous treatment history and cirrhosis status*. It was also not consistent with the majority of the evidence presented in Section B of the re-submission.

2.4 The ESC noted the sponsor's clarification in the PSCR (p1, presented below) that the intended regimen was DCV12+SOF12 for all genotypes, for treatment naïve and experienced, and for cirrhotic and non-cirrhotic patients, with consideration of adding RBV12 or extending treatment to 24 weeks (without RBV) in cirrhotic patients. The ESC noted that this is consistent with the proposed revised PI submitted to the TGA.

Table 1: Recommended dose regimens for DCV+SOF by patient subgroup

Genotype	Dosing	± Ribavirin	Duration	Price per patient
GT1	*DCV(60mg)+ SOF (400mg)*	*No§*	*12 weeks§*	*$[redacted]*
GT2	*DCV(60mg)+ SOF (400mg)*	*No§*	*12 weeks§*	*$[redacted]*
GT3	*DCV(60mg)+ SOF (400mg)*	*No§*	*12 weeks§*	*$[redacted]*
GT4	*DCV(60mg)+ SOF (400mg)*	*No§*	*12 weeks§*	*$[redacted]*
GT5	*DCV(60mg)+ SOF (400mg)*	*No§*	*12 weeks§*	*$[redacted]*
GT6	*DCV(60mg)+ SOF (400mg)*	*No§*	*12 weeks§*	*$[redacted]*

§ For cirrhotic patients: 12 weeks with ribavirin or 24 weeks without ribavirin should be considered (EASL guidelines, proposed update to Australian PI).[redacted]

2.5 The re-submission did not present Sections A, C, D or E. Only new clinical evidence was presented.

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

3 Background

3.1 TGA status at time of PBAC consideration: Daclatasvir was TGA registered in June 2015 for the treatment of CHC virus infection in adults with compensated liver disease (including cirrhosis) in combination with other medicinal products.

3.2 This is the second submission of daclatasvir to the PBAC for the treatment of CHC infection, irrespective of genotype, treatment history or cirrhosis status.

3.3 The first submission was considered by the PBAC in March 2015. PBAC recommended the listing of daclatasvir in combination with sofosbuvir for treatment of genotype 1 CHC in treatment naïve non-cirrhotic patients and for the treatment of

* European Association for the Study of the Liver (2015), American Association for the Study of Liver Diseases/Infectious Diseases Society of America (2015)

genotype 3 CHC, on the basis of acceptable cost effectiveness over no treatment (paragraphs 7.1 and 7.2 5.06 Daclatasvir Public Summary Document (PSD) March 2015 PBAC Meeting). 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 (paragraph 7.4, 5.06 Daclatasvir PSD, March 2015 PBAC Meeting).

3.4 The re-submission presented additional clinical evidence to support the claim that the effectiveness and safety of DCV+SOF is consistent across all genotypes and hard-to-treat patient populations, including treatment experienced patients, patients with cirrhosis, and patients with HCV and human immunodeficiency virus (HIV) co-infection.

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

4 Clinical place for the proposed therapy

4.1 This was not changed from the previous submission.

5 Comparator

5.1 The re-submission did not nominate any comparator.

5.2 The March 2015 PBAC Meeting PSD for daclatasvir states that, 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 ledipasvir/sofosbuvir (LDV/SOF) and sofosbuvir are likely to become the standard of care for almost all patients treated for CHC and that the listing of daclatasvir could only progress if sofosbuvir is available on the PBS (paragraph 7.7, 5.06 Daclatasvir PSD – March 2015 PBAC Meeting).

5.3 At the time of the re-submission, no interferon-free regimens had been recommended for listing on the PBS for treatment of CHC patients with HCV genotypes 4-6. Prior to the recommendation to list any all-oral CHC treatment regimens, the PBAC considered that the appropriate comparator was no treatment in view of the broader context of infected individuals whose treatment preference is interferon-free therapies (paragraph 7.5, 5.17 Sofosbuvir, PSD – July 2014 PBAC meeting).

5.4 Therefore, the most appropriate comparators for each of the HCV genotypes for which extension of the approved listing was requested, based on the dosage recommendations in the relevant TGA-approved PIs, were:

- Genotype 1 patients:
  - Treatment naïve patients with cirrhosis: LDV/SOF for 12 weeks;
  - Treatment experienced patients without cirrhosis: LDV/SOF for 12 weeks;
  - Treatment experienced patients with cirrhosis: LDV/SOF for 24 weeks;
- Genotype 2 patients: SOF plus RBV for 12 weeks; and

- Genotype 4-6 patients: no treatment. The ESC recalled that at its March 2015 meeting, the PBAC recommended the listing of sofosbuvir (when in combination with peg-interferon and ribavirin, 12 weeks) for the treatment of Genotype 3, 4, 5 and 6 CHC. As this regimen includes peg-interferon, the ESC considered that the appropriate comparator for this patient population was 'no treatment' in view of the broader context of infected individuals whose treatment preference is interferon-free therapies.

6 PBAC consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

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

Clinical studies

6.3 The re-submission was based on two non-comparative studies, and data from European compassionate use programs (CUPs):

- ALLY 1: A non-comparative open-label study of DCV+SOF+RBV for 12 weeks in genotype 1-6 CHC patients with advanced cirrhosis or who were post-liver transplant;
- ALLY 2: An open-label study of DCV+SOF in HCV treatment naïve and treatment experienced patients co-infected with HCV and HIV, in which:
  - HCV treatment naïve patients were randomised 2:1 to receive DCV+SOF for either 12 or 8 weeks, and
  - HCV treatment experienced patients received 12 weeks of DCV+SOF;
- CUPs:
  - EU CUP: A multicentre CUP of DCV+SOF±RBV for 24 weeks in patients at high risk of liver decompensation or death within 12 months if left untreated, conducted in 5 European countries;
  - EU CUP - UK cohort: An early access program of SOF+NS5A inhibitors with or without RBV for 12 weeks in patients with decompensated HCV cirrhosis; Patients could be treated with either LDV/SOF, LDV/SOF+RBV, SOF+DCV or SOF+DCV+RBV, at the clinician's discretion. As the number of patients receiving each particular regimen was not reported, this study was of little relevance to the proposed listing), and
  - French ATU cohort[†]: A CUP of DCV+SOF±RBV for 12 or 24 weeks in HCV/HIV co-infected patients with advanced liver disease.

[†] ATU = Authorisation temporaire d'utilisation.

6.4 Details of the studies presented in the re-submission are provided in the table below.

Table 2: Studies and associated reports presented in the re-submission

Study ID	Protocol title/ Publication title	Publication citation
Non-comparative studies		
ALLY 1	Final Clinical Study Report for Study AI444215: A phase 3 evaluation of daclatasvir, sofosbuvir, and ribavirin in genotype 1-6 chronic hepatitis C infection subjects with cirrhosis who may require future liver transplant and subject post-liver transplant.	April 2015
ALLY 2	Final Clinical Study Report for Study AI444216: A phase 3 evaluation of daclatasvir plus sofosbuvir in treatment naïve and treatment experienced chronic hepatitis C (genotype 1, 2, 3, 4, 5, or 6) subjects co-infected with human immunodeficiency virus.	April 2015
EU CUP (EU CUP AI444-237),	European multicentre compassionate use program for daclatasvir in combination with sofosbuvir with or without ribavirin for the treatment of subjects with chronic hepatitis C. Interim analysis: cut-off date 26 March 2015. Welzel TM, Herzer K, *et al.* Daclatasvir plus sofosbuvir with or without ribavirin for the treatment of HCV in patients with severe liver disease: interim results of a multicentre compassionate use program.	The International Liver Congress 2015. 50th annual meeting of the European Association for the Study of the Liver 2015. Poster P0772.
EU CUP – UK cohort* (EU CUP AI444-237)t	Compassionate use program for the treatment of decompensated HCV cirrhosis in patients with diverse genotypes in the UK: 12 weeks sofosbuvir and NS5A inhibitors with/without ribavirin is effective in HCV genotypes 1 and 3	NHS England. Clinical commissioning Policy Statement: sofosbuvir + daclatasvir/ledipasvir ± ribavirin for defined patients with hepatitis C. *No publication citation was provided for the results presented in the re-submission.*
French ATU cohort (AI444-258)	French multicentre compassionate use program for daclatasvir in combination with sofosbuvir with or without ribavirin in patients with HIV-HCV co-infection. Interim analysis.	None provided
TOSDAR**	Protocol: Transplant outcomes of sofosbuvir plus daclatasvir with or without ribavirin in advanced hepatitis C cirrhosis via Australian (and NZ) compassionate use programs.	November 2014

ATU = Authorisation temporaire d'utilisation; CUP = Compassionate use program; EU = European; HCV = hepatitis C virus; HIV = human immunodeficiency virus; UK = United Kingdom

* Reported as the English Early Access Program (EAP) in Appendix 1 to the re-submission

** Excluded as data were not yet available. Data were expected to be released by the end of 2015.

Source: Table 3, p4 of the submission and Table 5, p4 Appendix 1 to the re-submission.

6.5 In Appendix 1, the re-submission presented an indirect comparison of sustained virologic response at follow-up Week 12 (SVR12) for DCV+SOF12 and other all-oral treatment CHC regimens in HCV/HIV co-infected patients. No details were provided in the re-submission for the studies from which the SVR12 rates for other treatment regimens were sourced (see Section B(ii).2 of the commentary). Given the lack of information provided in the re-submission and the considerable potential for confounding inherent in any indirect comparison, these unadjusted indirect comparisons between studies were highly uncertain and should be interpreted with caution.

6.6 The key features of the included studies are summarised in the table below.

Table 3: Key features of the included evidence

Study/intervention	N	Design/duration	Risk of bias	Patient population	Outcome
ALLY 1 DCV+SOF+RBV 12	113[a]	SA, OL 24 weeks post treatment	Uncertain[c]	CHC patients with advanced cirrhosis or post-liver transplant recurrence of HCV	SVR12 (TD or TND)
ALLY 2 DCV+SOF12 or DCV+SOF 8	203[b]	R, OL 24 weeks post treatment	Low[d]	HCV treatment naïve or –experienced patients co-infected with HCV and HIV	SVR12 (TD or TND)
EU CUP DCV+SOF 24 or DCV+SOF+RBV 24	486[e]	Case series 12 weeks post treatment	High	CHC patients with high risk of liver decompensation or death within 12 months if left untreated	SVR12 (TD or TND)
French ATU program DCV+SOF±RBV 12 or 24	727[f]	Case series 12 or 24 weeks post treatment	High	HCV/HIV co-infected patients with advanced liver disease	SVR12[g]

CHC = chronic hepatitis C; DCV = daclatasvir; HCV = hepatitis C virus; HIV = human immunodeficiency virus; OL=open label; R = randomised; RBV = ribavirin; SA = single-arm; SOF = sofosbuvir; SVR12 = sustained virological response at Week 12 post-treatment.

[a] A total of 113 patients were treated, 3 with treatment extension after liver transplant. Of the 110 patients who did not have their treatment extended, 108 (98%) completed the 12 week treatment period. Patients who relapse within 12 weeks post-treatment were counted as non-responders (p681, ALLY 1 CSR)

[b] A total of 238 patients were enrolled in the study, of which 35 (15%) were not treated. Of the 203 patients treated, 199 (98%) completed assigned treatment. 201 patients completed the follow up week 12 visit.

[c] Results for SVR12 (target not detected (TND)) were not provided for ALLY 1. In EU CUP, which also included patients with advanced disease, 32% of patients who achieved SVR12 (target detected (TD) or TND) still had detectable HCV ribonucleic acid (RNA) at follow-up Week 12 (see point 6.8).

[d] The risk of bias in the assessment of SVR12 was relatively low, given that SVR12 is objective, the loss to follow-up was low, and all treated patients were included in the analysis (missing data were imputed using a next value carried back approach). All patients who achieved SVR12 (TD or TND) did not have detectable HCV RNA at follow-up Week 12 (i.e. achieved SVR12 TND). The assessment of adverse events may be subject to high risk of bias given the open label nature of the study design.

[e] A total of 486 patients were enrolled of which 482 were treated. Seventy (14%) patients discontinued treatment. The interim primary effectiveness analysis was based on all treated patients who had reached post-treatment week 12. Only 155 patients were included in the primary effectiveness analysis. There was some uncertainty about how patients who discontinued treatment were handled appropriately in the analyses.

[f] a total of 733 patients were enrolled, baseline characteristics were provided for 727 patients, while SVR12 results were provided for 57 (8%) of patients. There is insufficient information provided on the number of patients who discontinued treatment or were lost to follow-up, and how these patients were handled in the analyses, to assess the risk of bias.

[g] The definition of SVR12 was not reported.

Source: compiled during the evaluation

6.7 The outcomes for the CUP studies were based on poorly defined subgroups, for which neither baseline characteristics nor the patient disposition were available. There was considerable uncertainty regarding which patients were included in the effectiveness analyses and how patients who discontinued treatment were handled. Therefore, there was considerable risk of bias in the outcomes reported for these studies.

6.8 ALLY 1 and ALLY 2 were considered to form the main basis of the re-submission. Due to the limited information provided for the CUPs, the inability to verify the data, and the high risk of bias in these studies, the CUP studies are considered to provide supporting evidence only.

Comparative effectiveness

6.9 The primary outcome in all studies was SVR12, target detected (TD)[‡] or target not detected (TND). In EU CUP, which included patients with advanced disease, 32% of patients who achieved SVR12 (TD or TND) still had detectable HCV ribonucleic acid (RNA) at follow-up Week 12[§]. In contrast, in ALLY 2, which included patients with HCV/HIV co-infection, all patients who achieved SVR12 (TD or TND) did not have detectable HCV RNA at follow-up Week 12 (i.e. achieved SVR12 TND) (Appendix 5.1B, pp2851-52 ALLY 2 CSR). This suggests that SVR12 (TD or TND) may not be a reliable surrogate outcome for viral clearance in patients with advanced disease. SVR12 (TND) results could not be located for ALLY 1. Provision of SVR12 (TND) or SVR24 data would provide more confidence in the results reported for these hard-to-treat patients. The ESC noted the sponsor's response in the PSCR (p2) which appeared to show that most of those on treatment achieved a TND response while on therapy, even for those who subsequently failed to achieve an SVR12. The ESC considered the response did not adequately address the request for data on the proportion of participants who achieved an SVR12 TD versus SVR12 TND, and therefore the uncertainty regarding the durability of the treatment response among patients with advanced cirrhosis remained.

6.10 The SVR12 (results from ALLY 1 and ALLY 2, categorised by patient subgroups for which extension of the approved PBS listing was requested, are summarised below. The results from CUP studies are presented in Section B(ii).6 of the commentary.

Table 4: Summary of SVR12 results, categorised by subgroups

	Treatment	SVR12* n/N (%) [95% CI]	Population
Genotype 1 treatment experienced (combined 1a and 1b)			
ALLY 1	Not reported		
ALLY 2	DCV+SOF12	43/44 (97.7%) [88.0%, 99.9%]	HCV/HIV co-infection
Genotype 2			
ALLY 1	DCV+SOF+RBV12	4/5 (80.0%) [28.4%, 99.5%]	Advanced cirrhosis
ALLY 2			
TN	DCV+SOF12	11/11 (100%) [71.5%, 100%]	HCV/HIV co-infection
TE	DCV+SOF12	2/2 (100%) [15.8%, 100%]	
Genotype 4			
ALLY 1	DCV+SOF+RBV12	4/4 (100%) [39.8%, 100%]	Advanced cirrhosis
ALLY 2			
TN	DCV+SOF12	1/1 (100%) [2.5%, 100%]	HCV/HIV co-infection
TE	DCV+SOF12	2/2 (100%)	

[‡] Patients with SVR12 (TD) had HCV RNA less than the lower limit of quantification (25 IU/mL) but above the lower limit of detection.

[§] Welzel TM, Herzer K*, et al.* Daclatasvir plus sofosbuvir with or without ribavirin for the treatment of HCV in patients with severe liver disease: interim results of a multicenter compassionate use program. EASL - The International Liver Congress Vienna, Austria 2015.

	Treatment	SVR12* n/N (%) [95% CI]	Population
		[15.8%, 100%]	
Genotype 5			
No data			
Genotype 6			
ALLY 1	DCV+SOF+RBV12	1/1 (100%) [2.5%, 100%]	Post-liver transplant
ALLY 2**			HCV/HIV co-infection
TN	DCV+SOF12	1/1 (100%)	The source of these data could not be located in the CSR.
TE	DCV+SOF12	2/2 (100%)	
Treatment experienced patients (all genotypes)			
ALLY 1			
Cirrhotic patients	DCV+SOF+RBV12	27/36 (75.0%) [57.8%, 87.9%]	Advance cirrhosis
Post-liver transplant	DCV+SOF+RBV12	29/31 (93.5%) [78.6%, 99.2%]	Post-liver transplant
ALLY 2	DCV+SOF12	51/52 (98.1%) [89.7%, 100%]	HCV/HIV co-infection
Cirrhotic patients			
ALLY 1			
Genotypes 1-4 and 6	DCV+SOF+RBV12	50/60 (83.3%) [71.5%, 91.7%]	Advance cirrhosis
Genotype 1	DCV+SOF+RBV12	37/45 (82.2%) [67.9%, 92.0%]	Advance cirrhosis
ALLY 2			
TN	DCV+SOF12	8/9 (88.9%) [51.8%, 99.7%]	HCV/HIV co-infection
TE	DCV+SOF12	14/15 (93.3%) [68.1%, 99.8%]	

DCV = daclatasvir; HCV = hepatitis C virus; HIV = human immunodeficiency virus; RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virologic response; TE = treatment experienced; TN = treatment naïve

* SVR defined as HCV RNA < lower limit of quantification (target detected or target not detected).

** The ALLY 2 CSR states that no patients with genotype 6 HCV infection were included in the study (p68 ALLY 2 CSR).

Source: Table constructed during the evaluation, based on data presented in Table 7, p11 and Table 8, p12 of the resubmission; Table 7.1-1 p64, Table S.5.1B p181, Table 7.3.2-1 p67, Table 7.3.4-1 p71 and Table 7.3.4-2 p72 ALLY 1 CSR; Table 7.1-1 p81, Table S.5.1B p228, Table 7.3.2-1 p84, Table 7.3.5-1 p93 ALLY 2 CSR.

6.11 The results from the CUPs supported the claim that DCV+SOF±RBV12/24 was effective in genotype 1-4 HCV patients and patients with advanced disease, but for many patient subgroups, the treatment regimens used in the CUPs were not consistent with those proposed in original submission in regard to duration of treatment and concomitant use of ribavirin. Further, there was considerable risk of bias in the results for these studies. The ESC noted the updated interim analysis of the EU CUP provided in the PSCR (p3) including 408 patients with an SVR12 result available. The ESC agreed with the commentary that limiting the effectiveness estimates to only those with an SVR12 result available is likely to result in bias in favour of treatment.

6.12 Overall, the results of the studies indicated that DCV+SOF±RBV was effective across all patient subgroups, apart from patients with genotype 5 HCV for whom no results were available. However, in ALLY 1 and ALLY 2, the sample size in many patient

subgroups was too small to accurately estimate the magnitude of the clinical benefit. Further, there was considerable risk of bias in the results reported for the CUPs.

6.13 A comparison of SVR12 outcomes for DCV+SOF12 and other all-oral CHC treatment regimens was presented in Table B(ii).6.5 of the commentary. Due to exchangeability issues between studies, the results of these unadjusted indirect comparisons were highly uncertain.

6.14 The pre-PBAC response provided the breakdown of SVR rates for treatment naïve cirrhotic GT1 CHC patients and for treatment experienced cirrhotic GT1 CHC patients from ALLY-1 (DCV+SOF+RBV 12) and ALLY-2 (DCV+SOF12).

Table 5: SVR rates from ALLY-1 & ALLY-2 specific to naïve and experienced cirrhotic GT1 patients

Cirrhotic patients	Prior HCV treatment status	SVR12
ALLY-1	Naïve (responders/treated)	16/18 (88.9%)
ALLY-1	Experienced (responders/ treated)	21/27 (77.8%)
ALLY-2	Naïve (responders/treated)	8/9 (88.9%)
ALLY-2	Experienced (responders/ treated)	12/13 (92.3%)

Source: pre-PBAC response.

Comparative harms

6.15 The key adverse events (AEs) in ALLY 1 and ALLY 2 are summarised below.

Table 6: Summary of key adverse events in ALLY 1 and ALLY 2

	ALLY 1		ALLY 2
	Cirrhotic N = 60 n (%)	Post-transplant N = 53 n (%)	All subjects N = 203 n (%)
Deaths	0	0	2 (1.0%)
Serious AEs	5 (9.4%)	10 (16.7%)	4 (2.0%)
AEs leading to discontinuation	5 (9.4%)	10 (16.7%)	0
Grade 3/4 AEs	15 (13.3%)		8 (3.9%)
Treatment-related AEs	71/113 (62.8%)		69/203 (34.0%)
Most common AEs (>10% total)			
Headache	9 (15.0%)	19 (35.8%)	23 (11.3%)
Fatigue	11 (18.0%)	15 (28.3%)	34 (16.7%)
Diarrhoea	5 (8.3%)	10 (18.9%)	
Nausea	10 (16.7%)	3 (5.7%)	26 (12.8%)
Anaemia	12 (20.0%)	10 (18.9%)	
Arthralgia	1 (1.7%)	7 (13.2%)	

AE = adverse event
Source: Table 8.1-1, p 77 and p88 ALLY 1 CSR; Table 8.1-1, p105 ALLY 2 CSR

6.16 The most common AEs reported in ALLY 1 and ALLY 2 were consistent with those reported in the March 2015 submission. The higher rate of serious AEs, Grade 3/4 AEs and AEs leading to discontinuation in ALLY 1 compared to ALLY 2 may have been due to the inclusion of ribavirin in the treatment regimen (as reflected in the

number of patients discontinuing ribavirin), the more advanced disease status of patients in ALLY 1, and the fact that 25% of patients in ALLY 2 only received 8 weeks of treatment.

Benefits/harms

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

6.18

Table 7: Summary of comparative benefits and harms for DCV+SOF±RBV relative to No treatment

Patient group*	Comparison	Benefits (SVR12)**	Harm**
Genotype 1, treatment experienced	for every 100 patients treated with DCV+SOF12 in comparison to no treatment	• Approximately 98 additional patients would be expected to achieve an SVR	• Approximately 17 additional cirrhotic patients and 9 additional post-liver transplant patients would experience a serious AE from treatment with DCV+SOF+RBV12; • Approximately 13 additional patients who have advanced cirrhosis or are post-liver transplant would experience a Grade 3/4 AE, from treatment with DCV+SOF+RBV12; • Approximately 2 additional patients who are co-infected with HCV/HIV would experience a serious AE from treatment with DCV+SOF12; • Approximately 4 additional patients who are co-infected with HCV/HIV would experience a Grade 3/4 AE, from treatment with DCV+SOF12;
Genotype 1 cirrhotic patients	for every 100 patients treated with DCV+SOF+RBV12 in comparison to no treatment	• Approximately 82 additional patients would be expected to achieve an SVR	
Treatment experienced cirrhotic patients (all genotypes)* **	for every 100 patients treated with DCV+SOF+RBV12 in comparison to no treatment	• Approximately 75 additional patients would be expected to achieve an SVR	
Treatment experienced (all genotypes), irrespective cirrhosis status** **	for every 100 patients treated with DCV+SOF12 in comparison to no treatment:	• Approximately 98 additional patients would be expected to achieve an SVR	
Cirrhotic patients (all genotypes), irrespective previous treatment history*** **	for every 100 patients treated with DCV+SOF+RBV12 in comparison to no treatment	• Approximately 83 additional patients would be expected to achieve an SVR	

DCV+SOF12 = daclatasvir in combination with sofosbuvir for 12 weeks; DCV+SOF+RBV12 = daclatasvir and sofosbuvir in combination with ribavirin for 12 weeks; SVR = sustained virologic response; AE = adverse event; HCV= hepatitis C virus; HIV = human immunodeficiency virus.

*Benefits/harms are not presented for genotypes 2, 4, 5 and 6 given that either the sample size of the subgroup is too small to provide an accurate estimate of the magnitude of benefits or no data were available.

**Benefits/harms of DCV+SOF12 were observed from ALLY 2 in which all patients were co-infected with HCV/HIV; Benefits/harms of DCV+SOF+RBV12 were observed from ALLY 1 in which all patients had advanced cirrhosis or post-liver transplant recurrence of HCV.

*** 75% had genotype 1 HCV

**** 85% had genotype 1 HCV

***** 75% had genotype 1 HCV

Source: compiled during the evaluation.

Clinical claim

6.19 The re-submission claimed that the efficacy and safety of DCV+SOF was consistent across genotypes and hard-to-treat patient groups. The clinical evidence supported the claim that DCV+SOF (±RBV) was effective across HCV genotypes 1-4 and traditionally hard-to-treat patient groups, including treatment experienced patients and patients with cirrhosis:

- There was sufficient evidence to support the claim that:
  - DCV+SOF12 was highly effective in treatment experienced genotype 1-4 HCV patients with HCV/HIV co-infection (85% of whom had genotype 1 HCV);
  - DCV+SOF+RBV12 was highly effective in genotype 1-4 cirrhotic patients (Child-Pugh Class A and B, 80% genotype 1 HCV) and post-liver transplant patients (95% genotype 1 HCV);
- The ESC considered that the submitted evidence for DCV12+SOF12 from ALLY-2 supported a claim of non-inferiority to LDV/SOF12 among treatment experienced non-cirrhotic GT1 CHC patients by naïve indirect comparison.
- Submitted evidence for DCV12 + SOF12 was insufficient to support a claim of:
  - non-inferiority against LDV/SOF12 for treatment naïve GT1 CHC patients with cirrhosis
  - non-inferiority against LDV/SOF24 for treatment experienced GT1 CHC patients with cirrhosis
  - non-inferiority against RBV12+SOF12 for GT2 CHC patients
  - high effectiveness compared to no treatment against GT4-6 CHC patients
- The ESC noted that participants enrolled in ALLY-1 had advanced cirrhosis or were post-transplant limiting indirect comparison with treatment responses among cirrhotic patients from other studies. Submitted evidence for DCV12 + SOF12 + RBV 12 was insufficient to support a claim of:
  - non-inferiority against LDV/SOF24 for treatment experienced GT1 CHC patients with cirrhosis
  - non-inferiority against RBV12+SOF12 for GT2 CHC patients with cirrhosis
  - high effectiveness compared to no treatment against GT4-6 CHC patients with cirrhosis
- Submitted evidence for DCV24 + SOF24 was insufficient to support a claim of:
  - non-inferiority against LDV/SOF24 for treatment experienced GT1 CHC patients with cirrhosis
  - non-inferiority against RBV12+SOF12 for GT2 CHC patients with cirrhosis
  - high effectiveness compared to no treatment against GT4-6 CHC patients with cirrhosis
- The ESC considered the evidence provided in the CUPs was insufficient for supporting a claim of non-inferiority over current PBAC recommended CHC therapies for GT1 and GT2 or for quantifying the size of benefit of therapy for GT4-6 over no treatment.
- The sample size was too small to provide an accurate estimate of the magnitude of the clinical benefit of DCV+SOF12 in genotype 2 and 4 HCV patients and cirrhotic patients, or of DCV+SOF±RBV (12 or 24 weeks) in patients with genotypes 2 and 4 HCV; and

- There was no evidence for the effectiveness of DCV+SOF±RBV in patients with genotype 5 HCV and the evidence for genotype 6 HCV was based on one patient. However, these HCV genotypes only represent approximately 2% of the Australian CHC population**.

6.20 No evidence was presented in the re-submission to support the claim that the safety of DCV+SOF was consistent across all patient groups.

6.21 The ESC noted the publication of Backus LI et al. Effectiveness of sofosbuvir-based regimens in genotype 1 and 2 hepatitis C virus infection in 4026 U.S. Veterans. Alimentary Pharmacology and Therapeutics. 2015. While the study did not include patients treated with daclatasvir, the ESC noted the conclusion in this real-world patient population that SVR rates were lower than in clinical trials.

6.22 The PBAC considered that the evidence in the submission and the pre-PBAC response supported a claim of similar efficacy and similar safety to LDV/SOF12 for in the following patient groups:

- GT1 treatment experienced non-cirrhotic;
- GT1 treatment naïve cirrhotic; and
- GT1 treatment experienced cirrhotic

Economic analysis

6.23 The re-submission did not present any economic analysis.

***Drug cost/patient/course*:**

6.24 The re-submission did not present any proposed price. The drug cost/patient/course is contingent on the price of sofosbuvir.

Estimated PBS usage & financial implications

6.25 This re-submission is not being considered by DUSC. The re-submission did not present any estimated PBS usage and financial implications.

6.26 The PBAC confirmed their view from the March 2015 meeting, and recommended that an RSA should consist of a cap on expenditure, with a [redacted]% rebate for budget certainty.

7 PBAC Outcome

7.1 The PBAC recommended to expand the Authority Required listing of daclatasvir in combination with sofosbuvir for the treatment of all patients with Genotype 1 and Genotype 3 chronic hepatitis C (CHC).

7.2 In making this recommendation, the PBAC recalled that daclatasvir in combination with sofosbuvir was recommended for Genotype 1 treatment naïve non-cirrhotic and Genotype 3 chronic hepatitis C patients at its March 2015 PBAC meeting. The PBAC

** Bruggmann P, Berg T, et al. Historical epidemiology of hepatitis C virus (HCV) in selected countries. Journal of viral hepatitis. 2014;21 Suppl 1:5-33.

reiterated that there was no basis on which to make a cost effectiveness recommendation for daclatasvir in combination with sofosbuvir over ledipasvir/sofosbuvir (Genotype 1) or sofosbuvir in combination with ribavirin (Genotype 3).

7.3 Based on the clinical evidence provided in the re-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: Genotype 2 CHC patients, Genotype 4 CHC patients, Genotype 5 CHC patients and Genotype 6 CHC patients.

7.4 The PBAC noted from the pre-PBAC response that the sponsor acknowledged the lack of sufficient data to support listing for Genotype 2 CHC patients, Genotype 4 CHC patients, Genotype 5 CHC patients and Genotype 6 CHC patients.

7.5 The PBAC noted since the consideration of daclatasvir at the March 2015 meeting, the final product information was available and included the following dosing recommendations:

- Genotype 1 (No prior treatment, or failed peginterferon alfa/ribavirin): Consider adding ribavirin to the DAKLINZA/sofosbuvir 12-week regimen or prolonging treatment duration to 24 weeks for patients with cirrhosis.
- Genotype 1 (Failed protease inhibitor and peginterferon /ribavirin): daclatasvir and sofosbuvir for the duration of 24 weeks.
- Genotype 3 (No prior treatment, or failed sofosbuvir/ribavirin or peginterferon alfa/ribavirin): Consider prolonging treatment duration to 24 weeks for patients with cirrhosis.
- 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.

7.6 The PBAC considered that the listing should enable patients to be treated with the most appropriate treatment regimen for their disease status. The PBAC reiterated that the cost of a course of treatment should be [redacted] duration or dose of daclatasvir required.

7.7 The PBAC noted that no additional financial impact is expected from the expansion of the listing of daclatasvir in combination with sofosbuvir over the financial impact of the listing of the previously recommended IFN-free treatments for CHC. This is because daclatasvir in combination with sofosbuvir is expected to directly substitute for other CHC treatment regimens.

7.8 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 this meeting and at the March 2015 meeting, daclatasvir should not be treated as interchangeable with other recommended treatments of CHC on an individual patient basis.

7.9 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.

7.10 The PBAC reaffirmed that the Safety Net 20 Day Rule should apply to all the interferon-free DAA regimens, in line with the recommendations at the July 2015 meeting.

7.11 The resubmission is not eligible for an Independent Review, because the PBAC made a positive recommendation.

7.12 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 recent submissions for all oral treatments, 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.

Outcome
Recommended

8 Recommended listing

8.1 Restriction for treatment of Genotype 1 and Genotype 3 CHC 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 acknowledges the work done by all stakeholders involved in bringing access to daclatasvir for Australian patients via the PBS. While the sponsor believes a pan-genotypic PBS listing for daclatasvir would ensure effective therapies are available for all Australian HCV patients, it is encouraged that this medicine will soon be available to treat Australian patients with GT1 or GT3 disease.