

**5.14 SOFOSBUVIR with VELPATASVIR,
Tablet containing 400 mg sofosbuvir with 100 mg velpatasvir,
Epclusa®,
Gilead Sciences Pty Ltd.**

1 Purpose of Application

- 1.1 The submission requested General Schedule (Section 85) and Section 100 (Highly Specialised Drugs Program) Public and Private Hospital Authority Required listings for sofosbuvir with velpatasvir fixed-dose combination (FDC) for the treatment of chronic hepatitis C virus (HCV) infection in adults.

2 Requested listing

- 2.1 The requested listings are provided below. The Secretariat proposed wording consistent with other drugs currently listed *General Statement for Drugs for the Treatment of Hepatitis C* (the *General Statement*). The Secretariat also proposed that the prescriber type should include medical practitioners experienced in the treatment of hepatitis C, in line with changes to the *General Statement* that were implemented on 1 November 2016.

Name, Restriction, Manner of administration and form	Max qty packs	Max qty units	No. of Rpts	Dispensed Price for Max. Qty (requested published price)	Proprietary Name and Manufacturer
SOFOSBUVIR / VELPATASVIR 400mg / 100mg tablet, 28	1	28	2	S100 Public: \$ [REDACTED] S100 Private: \$ [REDACTED] S85 General: \$ [REDACTED]	Gilead Epclusa® Sciences Pty Ltd

Category/ Program:	General Schedule and S100 HSD (Public and Private)
PBS Indication:	Chronic HCV infection
Treatment criteria:	Must be treated by a gastroenterologist, hepatologist or infectious diseases physician experienced in the treatment of chronic hepatitis C infection; or in consultation with a gastroenterologist, hepatologist or infectious diseases physician experienced in the treatment of chronic hepatitis C infection. The following information must be provided at the time of application and documented in the patient's medical records: a) evidence of chronic hepatitis C infection (repeatedly antibody to hepatitis C virus (anti-HCV) positive and hepatitis C virus ribonucleic acid (HCV RNA) positive).
Clinical criteria:	Patient must meet the criteria set out in the General Statement for Drugs for the Treatment of Hepatitis C, AND Patient must be taking this drug as part of a regimen set out in the matrix in the General Statement for Drugs for the Treatment of Hepatitis C, based on presence or absence of hepatic decompensation, AND The treatment must be limited to a maximum duration of 12 weeks.

- 2.2 The submission also proposed to amend the wording of the *General Statement* in terms of the information requirements and documentation, and to add a new “pan-genotypic” table to the treatment matrix (see Table 1).

Table 1: Hepatitis C – Pan-genotypic PBS treatment matrix

	TREATMENT NAÏVE or TREATMENT EXPERIENCED
Non-cirrhotic or compensated cirrhotic	SOFOSBUVIR/VELPATASVIR [12 weeks]
Decompensated liver disease	SOFOSBUVIR/VELPATASVIR and RBV [12 weeks]

Source: Table A-4, p30 of the submission

- 2.3 During the evaluation, the following was noted regarding the requested PBS-listing and proposed changes to the *General Statement* for Drugs for the Treatment of Hepatitis C:

- The PBAC has previously considered that it was inappropriate to restrict access, given the likely benefit of the [direct acting antiviral] agents across the full spectrum of patients with [chronic HCV infection], from those with early disease to those patients with existing liver cirrhosis and severe portal hypertension, decompensated liver disease, or patients post liver transplant (paragraph 7.15, ledipasvir/sofosbuvir Public Summary Document (PSD), March 2015 PBAC meeting). The proposed changes differentiate compensated from decompensated cirrhosis, and may effectively exclude patients with decompensated cirrhosis from accessing other treatment regimens (including the nominated main comparators, which are PBS-listed for use in those with cirrhosis, but not specifically for decompensated cirrhosis).
- The proposed changes to the *General Statement* did not require provision of information or documentation of the presence or absence of decompensated cirrhosis (as per the requested PBS-listing); and omitted the assessment of cirrhosis status for pan-genotypic treatments.
- Eplclusa[®] (i.e. sofosbuvir/velpatasvir FDC) was identified as “pan-genotypic”; defined as “...whereby the dose and treatment duration are not influenced by the patients’ HCV genotype”. This definition may not be appropriate, and there are other agents that are pan-genotypic based on their pharmacological actions. The Pre-PBAC Response (p2) reiterated that sofosbuvir/velpatasvir FDC is pan-genotypic in the sense that it is a *single* tablet regimen effective against all six HCV genotypes, whilst other DAAs must be co-administered with other drugs to be effective against multiple genotypes.
- The proposed framing of the “pan-genotypic” treatment matrix may effectively exclude patients with decompensated cirrhosis who cannot tolerate or have contraindications to ribavirin from accessing PBS-subsidised sofosbuvir/velpatasvir FDC. The results from ASTRAL-4 (patients with decompensated cirrhosis) demonstrated that alternative sofosbuvir/velpatasvir FDC regimens without ribavirin were less effective. ASTRAL-4 also reported suboptimal adherence to protocol-defined ribavirin.

- 2.4 The PSCR (p1) stated that the differentiation was proposed “simply to facilitate the identification of evidence based recommendations in these severely ill patients and differentiate the requirement to add ribavirin” to sofosbuvir/velpatasvir FDC uniquely in patients with decompensated cirrhosis.

- 2.5 Listing was requested on cost-minimisation basis to the nominated comparators based on HCV genotype and cirrhosis status.

- 2.6 The sponsor indicated a willingness to engage in discussions with the Department regarding potential Special Pricing Arrangements.

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

3 Background

- 3.1 **TGA status at the time of PBAC consideration:** The submission was made under TGA/PBAC Parallel Process. At the time of the PBAC meeting, the TGA Delegate's Overview was available. At the time of the ESC advice and the evaluation, the Clinical Evaluation Report was available.

- 3.2 This was the first submission requesting PBS-listing of sofosbuvir/velpatasvir FDC.

- 3.3 A concurrent submission seeking to expand the PBS-listing of the ledipasvir/sofosbuvir FDC was withdrawn prior to consideration at the November 2016 PBAC meeting.

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

4 Clinical place for the proposed therapy

- 4.1 Hepatitis C is a blood-borne inflammatory liver disease caused by HCV, with around 75-80% of people exposed to HCV developing chronic infection which may lead to cirrhosis, liver failure, hepatocellular carcinoma and death. Approximately 230,000 people in Australia were estimated to be living with chronic HCV infection in 2014 (Kirby 2015). The sofosbuvir/velpatasvir FDC is an alternative treatment option to those already listed on the PBS for the treatment of this condition.

5 Comparator

- 5.1 The submission nominated one main comparator for the each of the identified subgroups by HCV genotype and cirrhosis status based on the regimen most frequently prescribed (see Table 2).

- 5.2 The ESC advised that the submission did not conduct a thorough review of appropriate comparators, and that in at least one instance there was an omission of data for a nominated comparator. The ESC considered that the submission did not present the totality of evidence available. The Pre-PBAC Response (p2) argued that while the sponsor "was not averse to presenting the totality of the data, this would have unnecessarily complicated and prolonged the evaluation, without providing any further relevant information to inform and assist the PBAC's decision making."

Table 2: Nominated main comparators by HCV genotype and cirrhosis status

HCV Gt	Non-cirrhotic patients	Compensated cirrhosis	Decompensated cirrhosis
1	Ledipasvir/sofosbuvir FDC (8 or 12 weeks)	Ledipasvir/sofosbuvir FDC (12 or 24 weeks)	Daclatasvir + sofosbuvir + ribavirin (12 weeks)
2	Sofosbuvir + ribavirin (12 weeks)	Sofosbuvir + ribavirin (12 weeks)	[None specified]
3	Daclatasvir + sofosbuvir (12 weeks)	Daclatasvir + sofosbuvir (24 weeks)	Daclatasvir + sofosbuvir + ribavirin (24 weeks)
4, 5, 6	Sofosbuvir + peg-IFN & ribavirin (12 weeks)	Sofosbuvir + peg-IFN & ribavirin (12 weeks)	[None specified]

Source: Adapted from Table A-6, p44 of the submission

Abbreviations: FDC = fixed-dose combination; Gt = genotype; HCV = hepatitis C virus; peg-IFN = peginterferon alfa-2a

5.3 The PBAC viewed that a range of potential comparators existed (that is, all regimens in the *General Statement*) and agreed with the ESC that the submission had not presented the totality of the evidence available. In particular, the PBAC noted that sofosbuvir plus ribavirin for 24 weeks may be a potential comparator for genotype 3 patients, and that the submission presented a head-to-head trial (ASTRAL-3) that could inform such a comparison. In that context, the sponsor’s Pre-PBAC Response acknowledges that the PBAC has previously accepted that daclatasvir plus sofosbuvir (12 weeks) is non-inferior to sofosbuvir plus ribavirin (24 weeks) in GT3 (daclatasvir PSD, March 2015).

5.4 The PBAC also noted that in the absence of demonstrated superior comparative effectiveness or comparative safety of sofosbuvir/velpatasvir FDC over alternative regimens, there is no basis for sofosbuvir/velpatasvir FDC to have a cost advantage over the relevant lowest priced alternative regimen in the *General Statement*.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (3) and organisations (10) via the Consumer Comments facility on the PBS website. The comments described how this drug will improve cure rates, reduce treatment duration and offer simpler administration with fewer side effects. The simplified administration, and the fact that this drug can be used against all genotypes, may result in more prescribing by GPs. The comments also noted that this drug would provide an interferon-free treatment option for some patients with genotypes 4-6.

6.3 The PBAC noted the advice received from the following organisations with regards to the three submissions for chronic hepatitis C treatment made to the PBAC [this submission and items 5.11 paritaprevir + sofosbuvir + ombitasvir and 6.03 ledipasvir + sofosbuvir (item 6.03 was withdrawn prior to PBAC consideration)]:

- Hepatitis Australia

- Haemophilia Foundation Australia
- Hepatitis NSW
- ACON
- The Haymarket Foundation
- Hepatitis ACT
- Network of Alcohol and Other Drugs Agencies
- Sex Workers Outreach Project
- St Vincent de Paul Society NSW
- We Help Ourselves

The PBAC noted the view shared amongst most organisations that these new treatments will help ensure as many GPs as possible are able to prescribe the new direct acting antivirals, that all people living with hepatitis C have access to interferon-free treatment, and that there are multiple treatment options for each hepatitis C genotype. The PBAC also noted the advice that there are certain populations living with both HCV and other health conditions, and that successful treatment of HCV would greatly reduce the complexity of the healthcare needs of these groups.

Clinical trials

- 6.4 The submission was based on four key Phase III trials and one supplementary single-arm study. The details of the trials and study are summarised in Table 4. The submission then presented a series of naïve comparisons comparing:
- No cirrhosis and compensated cirrhosis
- Sofosbuvir/velpatasvir FDC (12 weeks) versus ledipasvir/sofosbuvir (8, 12 or 24 weeks) among patients with chronic HCV genotype 1 infection.
 - Sofosbuvir/velpatasvir FDC (12 weeks) versus daclatasvir plus sofosbuvir (12 weeks) among patients with chronic HCV genotype 3 infection.
 - Sofosbuvir/velpatasvir FDC (12 weeks) versus sofosbuvir plus peginterferon plus ribavirin (12 weeks) among patients with chronic HCV genotypes 4 to 6 infection.
- Decompensated cirrhosis
- Sofosbuvir/velpatasvir FDC plus ribavirin (12 weeks) versus daclatasvir plus sofosbuvir plus ribavirin (12 weeks) and ledipasvir/sofosbuvir FDC plus ribavirin (12 weeks) among patients with chronic HCV infection.
- 6.5 ASTRAL-2 provided a head-to-head comparison of sofosbuvir/velpatasvir FDC versus the nominated comparator of sofosbuvir plus ribavirin for 12 weeks in patients with chronic HCV genotype 2 infection, with or without compensated cirrhosis. ASTRAL-3 was a head-to-head trial of sofosbuvir/velpatasvir FDC versus sofosbuvir plus ribavirin for 24 weeks in patients with HCV genotype 3 with or without compensated cirrhosis.
- 6.6 Details of the sofosbuvir/velpatasvir FDC studies presented in the submission are provided in Table 3.

Table 3: Trials and associated reports presented in the submission

Study ID	Protocol title/ Publication title	Publication citation
Key randomised trials		
ASTRAL-1 GS-US-342-1138 NCT02201940	A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5816 Fixed Dose Combination for 12 Weeks in Subjects with Chronic HCV. Interim Clinical Study Report. Feld JJ, Jacobson IM, Hézode C, Asselah T, Ruane PJ, <i>et al</i> for the ASTRAL-1 Investigators. Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection.	8 September 2015 <i>N Engl J Med</i> 2015; 373(27): 2599-2607.
NCT02346721*	Asselah T, Shafran S, Bourgeois S, Lai C-L, Cramp M, <i>et al</i> . Sofosbuvir/Velpatasvir for 12 weeks in HCV-treated patients previously treated with placebo: results of the deferred treatment study [Poster (SAT-279)].	Presented at European Association for the Study of the Liver (EASL) 2016, Barcelona.
ASTRAL-2 GS-US-342-1139 NCT02220998	A Phase 3, Multicenter, Randomised, Open-Label Study to Compare the Efficacy and Safety of Sofosbuvir/GS-5816 Fixed Dose Combination for 12 Weeks with Sofosbuvir and Ribavirin for 12 Weeks in Subjects with Chronic Genotype 2 HCV Infection. Interim Clinical Study Report. Foster GR, Afdhal N, Roberts SK, Bräu N, Gane EJ, <i>et al</i> for the ASTRAL-2 and ASTRAL-3 Investigators. Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection.	11 August 2015 <i>N Engl J Med</i> 2015; 373(27): 2608-2617.
ASTRAL-3 GS-US-342-1140 NCT02201953	A Phase 3, Multicenter, Randomised, Open-Label Study to Compare the Efficacy and Safety of Sofosbuvir/GS-5816 Fixed Dose Combination for 12 Weeks with Sofosbuvir and Ribavirin for 24 Weeks in Subjects with Chronic Genotype 3 HCV Infection. Interim Clinical Study Report. Foster GR, Afdhal N, Roberts SK, Bräu N, Gane EJ, <i>et al</i> for the ASTRAL-2 and ASTRAL-3 Investigators. Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection.	8 October 2015 <i>N Engl J Med</i> 2015; 373(27): 2608-2617.
ASTRAL-4 GS-US-342-1137 NCT02201901	A Phase 3, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5816 Fixed-Dose Combination in Subjects with Chronic HCV Infection and Child-Pugh Class B Cirrhosis. Interim Clinical Study Report. Curry MP, O'Leary JG, Bzowej N, Muir AJ, Korenblat KM <i>et al</i> Curry, <i>et al</i> for the ASTRAL-4 Investigators. Sofosbuvir and Velpatasvir for HCV in Patients with Decompensated Cirrhosis.	13 October 2015 <i>N Engl J Med</i> 2015; 373(27): 2618-2628.
Supplementary study		
ASTRAL-5 GS-US-342-1202	A Phase 3, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/ Velpatasvir Fixed Dose Combination for 12 weeks in Subjects with Chronic Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV)-1 Coinfection. Clinical Study Protocol. Wyles D, Brau N, Kottlilil S, Daar E, Workowski K, <i>et al</i> . Sofosbuvir/Velpatasvir for 12 Weeks in Patients Coinfected With HCV and HIV-1: The ASTRAL-5 Study [presentation].	20 April 2015 Presented at European Association for the Study of the Liver (EASL) 2016, Barcelona.

Source: Table B-4, pp69-70 of the submission.

Note: Abstracts/presentations of conference proceedings were not included if a relevant peer-reviewed journal article was available.

*The trial ID was corrected during the evaluation

6.7 The key features of the sofosbuvir/velpatasvir FDC studies are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias ^c	Patient population			Intervention	Key outcome
				HCV Gt	Cirrhosis	Tx history		
Pivotal trials								
ASTRAL-1	741 ^a	R, DB, MC 24 weeks (deferred Tx– OL CO for PBO arm)	Low	1, 2, 4, 5, 6 (all Gt 5 allocated to SOF/VEL12)	Non-cirrhotic & compensated cirrhosis	Tx naïve & experienced	SOF/VEL12 vs PBO12	SVR12
ASTRAL-2	269	R, OL, MC 24 weeks	Low	2	Non-cirrhotic & compensated cirrhosis	Tx naïve & experienced	SOF/VEL12 vs SOF+RBV12	SVR12
ASTRAL-3	558	R, OL, MC 24 or 36 weeks	High ^b	3	Non-cirrhotic & compensated cirrhosis	Tx naïve & experienced	SOF/VEL12 vs SOF+RBV24	SVR12
ASTRAL-4	268	R, OL, MC 24 or 36 weeks	NA	All (no Gt 5 enrolled)	CPT class B decompensated cirrhosis	Tx naïve & experienced	SOF/VEL12 vs SOF/VEL+RBV12 vs SOF/VEL24	SVR12
Supplementary study								
ASTRAL-5	106	OL, MC, single arm 24 weeks	NA	HCV/HIV-1 co-infection			SOF/VEL12	SVR12
				All (no Gt 5 or 6 enrolled)	Non-cirrhotic & compensated cirrhosis	Tx naïve & experienced		

Source: constructed during the evaluation

Abbreviations: CO = crossover; CPT = Child-Pugh-Turcotte; DB = double-blind; Gt = genotype; HCV = hepatitis C virus; HIV = human immunodeficiency virus; MC = multi-centre; NA = not applicable; OL = open-label; R = randomised; PBO12 = placebo for 12 weeks; SOF+RBV12 = sofosbuvir plus ribavirin for 12 weeks; SOF+RBV24 = sofosbuvir plus ribavirin for 24 weeks; SOF/VEL12 = sofosbuvir/velpatasvir FDC for 12 weeks; SOF/VEL24 = sofosbuvir/velpatasvir FDC for 24 weeks; SOF/VEL+RBV12 = sofosbuvir/velpatasvir FDC plus ribavirin for 12 weeks; SVR12 = sustained virological response at 12 weeks following the completion of treatment; Tx = treatment

Note: Treatment experienced patients included those who have failed a peginterferon alfa plus ribavirin based regimen with or without an HCV protease inhibitor. The studies all had 24 weeks post-treatment follow-up, but only data from 12 weeks post-treatment from the interim reports were presented.

^a Patients with HCV genotype 1, 2, 4, or 6 were randomly assigned in a 5:1 ratio to receive either SOF/VEL12 or placebo.

^b There was differential discontinuation between arms in ASTRAL-3, with more patients in the comparator arm (sofosbuvir plus ribavirin for 24 weeks) not starting (5 patients vs 1 patient) or discontinuing (21 vs 2 patients) study drug.

^c identified during the evaluation

- 6.8 The submission presented results at 12 weeks following the completion of treatment from the interim reports. The results at 24 weeks following completion of treatment were not available.
- 6.9 The submission presented a series of unadjusted naïve comparisons. As discussed above, the evaluation and the ESC noted that the comparator data presented may not represent the totality of the evidence available. The submission did not present any information regarding risk of bias for the identified comparator studies, nor an assessment of the exchangeability of the studies included in the naïve comparisons. The submission did not present sufficient information to facilitate assessment of the exchangeability during the evaluation, as very limited information on the selected comparator studies was included (e.g. top-line description of the study design and treatment regimens without the doses of individual medicines). Sustained virological response at 12 weeks following the completion of treatment (SVR12) rates are affected by study design (including quality), inclusion criteria, baseline characteristics, outcome measures, and so forth. The submission only presented the point estimates of the SVR12 rates, with no measures of uncertainty. There was no

adjustment due to the lack of a common reference. No formal non-inferiority testing was conducted. Overall, the risk of bias of the presented naïve comparisons was high.

Comparative effectiveness

HCV genotype 1 infection with no cirrhosis or compensated cirrhosis

Table 5: Naïve comparison of SVR12 rates in HCV genotype 1 (no cirrhosis or compensated cirrhosis)

Study ID	Study phase	% cirrhosis	% treatment experienced	Treatment regimen	Duration (weeks)	SVR12	
						n/N	% (95% CI)
No cirrhosis							
ASTRAL-1	Phase III	0%	NR (mixed) ^c	SOF/VEL	12	251/255	98.4 (96.0, 99.6)
Everson (2015) ^c	Phase II	0%	0%	SOF/VEL	12	28/28	100 (87.7, 100)
ION-3	Phase III	0%	0%	LDV/SOF	8	119/123 ^a	96.7 (91.9, 99.1)
ION-3 & ION-1	Phase III	0%	0%	LDV/SOF	12	385/395 ^b	97.5 (95.4, 98.8)
ION-2	Phase III	0%	100%	LDV/SOF	12	83/87	95.4 (88.6, 98.7)
Cirrhosis							
ASTRAL-1	Phase III	100%	NR (mixed) ^c	SOF/VEL	12	72/73	98.6 (92.6, 100)
ION-1	Phase III	100%	0%	LDV/SOF	12	32/34	94.1 (80.3, 99.3)
ION-2	Phase III	100%	100%	LDV/SOF	24	22/22	100 (84.6, 100)
SIRIUS ^c	Phase II	100%	100%	LDV/SOF	24	75/77	97.4 (90.9, 99.7)
Treatment naïve							
ASTRAL-1	Phase III	NR (mixed) ^c	0%	SOF/VEL	12	214/218	98.2 (95.4, 99.5)
Everson (2015) ^c	Phase II	0%	0%	SOF/VEL	12	28/28	100 (87.7, 100)
ION-3	Phase III	0%	0%	LDV/SOF	8	119/123 ^a	96.7 (91.9, 99.1)
ION-3 & ION-1	Phase III	0%	0%	LDV/SOF	12	385/395 ^b	97.5 (95.4, 98.8)
ION-1	Phase III	100%	0%	LDV/SOF	12	32/34	94.1 (80.3, 99.3)
Treatment experienced							
ASTRAL-1	Phase III	NR (mixed) ^c	100%	SOF/VEL	12	109/110	99.1 (95.0, 100)
Pianko (2015) ^c	Phase II	26%	100%	SOF/VEL	12	27/27	100 (87.2, 100)
ION-2	Phase III	0%	100%	LDV/SOF	12	83/87	95.4 (88.6, 98.7)
ION-2	Phase III	100%	100%	LDV/SOF	24	22/22	100 (84.6, 100)
SIRIUS ^c	Phase II	100%	100%	LDV/SOF	24	75/77	97.4 (90.9, 99.7)

Source: Adapted from Table B-44, p121 of the submission; Bourlière *et al* (2015); Everson *et al* (2015); Pianos *et al* (2015)

Abbreviations: CI = confidence interval; HCV = hepatitis C virus; LDV/SOF = ledipasvir/sofosbuvir; NR = not reported; SOF/VEL = sofosbuvir/velpatasvir FDC; SVR12 = sustained virological response at 12 weeks following the completion of treatment

Note: Shaded cells represent sofosbuvir/velpatasvir FDC results. 95% CI calculated using Stata14 (binomial exact), during the evaluation

^a Baseline HCV RNA <6 million IU/mL

^b This value could not be verified from the reported source.

^c identified during the evaluation.

- 6.10 ASTRAL-1 did not report results by cirrhosis status and treatment history. Therefore, the results in Table 5 represent two separate subgroup analyses for sofosbuvir/velpatasvir FDC (cirrhosis versus no cirrhosis, treatment naïve versus treatment experienced); with corresponding data from the comparator studies included when relevant (i.e. comparator results were duplicated).
- 6.11 The evaluation considered that the presented naïve comparison should be interpreted with caution due to the high risk of bias and limitations outlined above, as well as the small patient numbers in some of the included arms (as low as 22 patients). While presentation of results stratified by cirrhosis status and treatment

history improve exchangeability, there were no results for sofosbuvir/velpatasvir FDC by cirrhosis status and treatment history.

HCV genotype 2 infection with no cirrhosis or compensated cirrhosis

Table 6: Primary analysis of ASTRAL-2: SVR12 (Full Analysis Set) in patients with HCV genotype 2 (no cirrhosis or compensated cirrhosis)

	SOF/VEL12	SOF+RBV12	Diff in % [95% CI] ^a
SVR12; n/N (%) [95% CI]	133/134 (99.3%) [95.9%, 100%]	124/132 (93.9%) [88.4%, 97.3%]	5.2% [0.2%, 10.3%]

Source: Adapted from Table B-25, p106 of the submission

Abbreviations: CI = confidence interval; SOF+RBV12 = sofosbuvir plus ribavirin for 12 weeks; SOF/VEL12 = sofosbuvir/velpatasvir FDC for 12 weeks; SVR12 = sustained virological response at 12 weeks following the completion of treatment

^a SOF/VEL12 versus SOF+RBV12

- 6.12 The results indicate that non-inferiority of sofosbuvir/velpatasvir FDC versus sofosbuvir plus ribavirin could be concluded, as the lower bound of the 95% CI (+0.2%) was greater than the pre-specified non-inferiority margin of -10%. A claim of non-inferiority of sofosbuvir/velpatasvir FDC versus sofosbuvir plus ribavirin among patients with HCV genotype 2 with no cirrhosis or compensated cirrhosis was supported despite concerns that the pre-specified non-inferiority margin included clinically important differences. However, the statistically significant differences in SVR12 rates may not be clinically relevant as the 95% CI included values that were unlikely to be clinically important.

HCV genotype 3 infection with no cirrhosis or compensated cirrhosis

Table 7: Naïve comparison of SVR12 rates in HCV genotype 3 (no cirrhosis or compensated cirrhosis)

Study ID	Study phase	Treatment regimen	Duration (weeks)	SVR12	
				n/N	% (95% CI)
No cirrhosis and treatment naïve					
ASTRAL-3	Phase III	SOF/VEL	12	160/163	98.2 (94.7, 99.6)
Everson (2015) ^a	Phase II	SOF/VEL	12	25/27	92.6 (75.7, 99.1)
ALLY-3	Phase III	DCV+SOF	12	73/75	97.3 (90.7, 99.7)
No cirrhosis and treatment experienced					
ASTRAL-3	Phase III	SOF/VEL	12	31/34	91.2 (76.3, 98.1)
Pianko (2015) ^a	Phase II	SOF/VEL	12	27/27	100 (87.2, 100)
ALLY-3	Phase III	DCV+SOF	12	32/34	94.1 (80.3, 99.3)
Cirrhosis and treatment naïve					
ASTRAL-3	Phase III	SOF/VEL	12	40/43	93.0 (80.9, 98.5)
No data [nominated comparator]	-	DCV+SOF	24	-	-
ALLY-3 [wrong comparator]	Phase III	DCV+SOF	12	11/19	57.9 (33.5, 79.7)
Cirrhosis and treatment experienced					
ASTRAL-3	Phase III	SOF/VEL	12	33/37	89.2 (74.6, 97.0)
Pianko (2015) ^a	Phase II	SOF/VEL	12	23/26	88.5 (69.8, 97.6)
No data [nominated comparator]	-	DCV+SOF	24	-	-
ALLY-3+[alternative comparator] ^a	Phase III	DCV+SOF+RBV	12	14/16	87.5 (61.7, 98.4)
ALLY-3+[alternative comparator] ^a	Phase III	DCV+SOF+RBV	16	12/14	85.7 (57.2, 98.2)

Source: Table B-44, p121 of the submission; Everson *et al* (2015); Pianko *et al* (2015)

Abbreviations: CI = confidence interval; DCV = daclatasvir; HCV = hepatitis C virus; NR = not reported; SOF = sofosbuvir; SOF/VEL = sofosbuvir/velpatasvir FDC; SVR12 = sustained virological response at 12 weeks following the completion of treatment

Note: Shaded cells represent sofosbuvir/velpatasvir FDC results. 95% CI calculated using Stata14 (binomial exact), during the evaluation.

^a added during the evaluation.

6.13 Among patients with HCV genotype 3, the submission claimed that sofosbuvir/velpatasvir FDC for 12 weeks demonstrated:

- A comparable SVR12 to daclatasvir plus sofosbuvir for 12 weeks among patients without cirrhosis.
- A higher SVR12 compared with daclatasvir plus sofosbuvir for 12 weeks among patients who were treatment naïve and with cirrhosis. However, the submission did not nominate this treatment regimen as the main comparator, rather daclatasvir plus sofosbuvir for 24 weeks.
- The submission did not locate results for daclatasvir plus sofosbuvir for 24 weeks in cirrhotic patients who were treatment experienced. The submission however argued that sofosbuvir/velpatasvir FDC demonstrated a high SVR12 (33/37; 89%) in this population. Therefore, it was not possible to assess the comparative claim versus daclatasvir plus sofosbuvir for 24 weeks.

Similarly, the presented naïve comparison should be interpreted with caution due to the high risk of bias and limitations outlined above, as well as the small patient numbers in some of the included arms. There was data asymmetry, with sparser comparator data.

6.14 The PBAC previously considered that it was reasonable to accept that daclatasvir plus sofosbuvir for 12 weeks was non-inferior in terms of comparative efficacy with sofosbuvir plus ribavirin for 24 weeks in treatment-naïve non-cirrhotic genotype 3 patients (daclatasvir PSD March 2015 PBAC meeting). The head-to-head trial in HCV genotype 3 (ASTRAL-3) provided a comparison of sofosbuvir/velpatasvir FDC versus sofosbuvir plus ribavirin (24 weeks).

Table 8: SVR12 (Full Analysis Set) for ASTRAL-3 in patients with HCV genotype 3 (no cirrhosis or compensated cirrhosis)

	SVR12; n/N (%) [95% CI]		Diff in % [95% CI] ^a
	SOF/VEL12	SOF+RBV24	
Overall	264/277 (95.3%) [92.1, 97.5%]	221/275 (80.4%) [75.2, 84.9%]	14.8% [9.6, 20.0%]
Cirrhosis status			
No cirrhosis	191/197 (97.0%) [93.5, 98.9%]	163/187 (87.2%) [81.5, 91.6%]	9.8% [4.2, 15.7%]
Compensated cirrhosis	73/80 (91.3%) [82.8, 96.4%]	55/83 (66.3%) [55.1, 76.3%]	25.0% [11.5, 37.2%]
Prior HCV treatment experience			
Treatment naïve	200/206 (97.1%) [93.8, 98.9%]	176/204 (86.3%) [80.8, 90.7%]	10.8% [5.3, 16.5%]
Treatment experienced	64/71 (90.1%) [80.7, 95.9%]	45/71 (63.4%) [51.1, 74.5%]	26.8% [12.2, 40.1%]

Source: Adapted from Table B-28, p108 of the submission

Abbreviations: CI = confidence interval; HCV = hepatitis C virus; SOF+RBV24 = sofosbuvir plus ribavirin for 24 weeks; SOF/VEL12 = sofosbuvir/velpatasvir FDC for 12 weeks; SVR12 = sustained virological response at 12 weeks following the completion of treatment

^a SOF/VEL12 versus SOF+RBV24

6.15 The results indicate that non-inferiority of sofosbuvir/velpatasvir FDC versus sofosbuvir plus ribavirin could be concluded as the lower bound of the 95% CI (+9.6%) was greater than the pre-specified non-inferiority margin of -10% (despite concerns that the pre-specified non-inferiority margin included clinically important differences). While the results were supportive of a claim of superiority, the PBAC agreed that these results should be interpreted with caution due to the open-label design, as well as the differential discontinuation and adherence between arms favouring sofosbuvir/velpatasvir FDC.

- 6.16 Among patients with HCV genotype 3 (ASTRAL-3), there was some variation in SVR12 rates associated with sofosbuvir/velpatasvir FDC treatment based on cirrhosis status and prior treatment experience, where SVR12 rates were highest for treatment naïve patients without cirrhosis (98.2%; 160/163) and lowest for treatment experienced patients with cirrhosis (89.2%; 33/37). Despite this, the differences in proportions between treatment arms were noticeably larger for the compensated cirrhosis and treatment experienced subgroups (see Table 8), mainly driven by the considerably lower SVR12 rates among those who received sofosbuvir plus ribavirin for 24 weeks. Other baseline characteristics associated with lower SVR12 rates included pre-treatment NS5A resistance-associated variants (RAVs) and pre-treatment HCV RNA $\geq 800,000$ IU/mL (while acknowledging that the small patients numbers for some subgroups precluded definitive conclusions). Relapse after treatment was associated with NS5A resistance (Y93H mutation) in all patients, which limits re-treatment options as this mutation affects the activity of all agents in this class (European public assessment report, 2016).

HCV genotypes 4 to 6 infection, with no cirrhosis or compensated cirrhosis

Table 9: Naïve comparison of SVR12 rates in HCV genotype 4 to 6 (no cirrhosis or compensated cirrhosis)

Study ID	Study design	HCV Gt	% cirrhosis ^b	% treatment experienced	Treatment regimen	Duration (weeks)	SVR12	
							n/N	% (95% CI)
Treatment naïve								
ASTRAL-1	Phase III	4	NR (mixed)	0%	SOF/VEL	12	64/64	100 (94.4, 100)
		5	NR (mixed)	0%	SOF/VEL	12	23/24	95.8 (78.9, 99.9)
		6	NR (mixed)	0%	SOF/VEL	12	38/38	100 (90.7, 100)
Everson (2015) ^b	Phase II	4-6	0%	0%	SOF/VEL	12	21/22	95.5 (77.2, 99.9)
NEUTRINO ^{a,b}	Phase III	4-6	6%	0%	SOF+PR	12	34/35	97.1 (85.1, 99.9)
Treatment experienced								
ASTRAL-1	Phase III	4	NR (mixed)	100%	SOF/VEL	12	52/52	100 (93.2, 100)
		5	NR (mixed)	100%	SOF/VEL	12	11/11	100 (71.5, 100)
		6	NR (mixed)	100%	SOF/VEL	12	3/3	100 (29.2, 100)
No data ^b	-	-	-	-	SOF+PR	12	-	-

Source: Adapted from Table B-44, p121 of the submission; Everson *et al* (2015); sofosbuvir SmPC provided with the submission

Abbreviations: CI = confidence interval; Gt = genotype; HCV = hepatitis C virus; NR = not reported; PR = peginterferon plus ribavirin; SOF = sofosbuvir; SOF/VEL = sofosbuvir/velpatasvir FDC; SVR12 = sustained virological response at 12 weeks following the completion of treatment

Note: Shaded cells represent sofosbuvir/velpatasvir FDC results. 95% CI calculated using Stata14 (binomial exact), during the evaluation.

^a 27/28 patients with HCV genotype 4 achieved SVR12. A single subject with genotype 5 and all 6 subjects with genotype 6 HCV infection achieved SVR12. The patient who did not achieve SVR12 had cirrhosis at baseline (only 2 patients in this subgroup had cirrhosis).

^b added during the evaluation

- 6.17 The submission extracted results from a study among treatment naïve patients for the comparator (NEUTRINO). Further stratification by cirrhosis status was inappropriate, as only two patients in the comparator trial had cirrhosis (one patient achieved SVR12).
- 6.18 Among patients with HCV genotypes 4 to 6, the submission claimed that sofosbuvir/velpatasvir FDC for 12 weeks resulted in higher SVR12 rates compared to sofosbuvir plus peginterferon plus ribavirin where data were available. This claim was

inadequately supported from the presented evidence; as there were no apparent differences in the SVR12 rates between sofosbuvir/velpatasvir FDC versus sofosbuvir plus peginterferon plus ribavirin. The naïve comparison was at high risk of bias and may not be valid (see paragraph 6.9). There was data asymmetry, where the comparator data were sparser. There were no comparator data for treatment-experienced patients, nor sufficient comparator data to facilitate comparison based on cirrhosis status.

HCV genotypes 1-6, with decompensated cirrhosis

Table 10: ASTRAL-4 (decompensated cirrhosis – CPT class B): SVR12 (Full Analysis Set)

Treatment regimen	SVR12; n/N (%) [95% CI]						
	Gt 1	Gt 2	Gt 3	Gt 4	Gt 5	Gt 6	Total
SOF/VEL 12 weeks	60/68 (88.2%) [78.1, 94.8%]	4/4 (100.0%) [39.8, 100%]	7/14 (50.0%) [23.0, 77.0%]	4/4 (100.0%) [39.8, 100%]	-	0	75/90 (83.3%) [74.0, 90.4%]
SOF/VEL +RBV 12 weeks	65/68 (95.6%) [87.6, 99.1%]	4/4 (100.0%) [39.8, 100%]	11/13 (84.6%) [54.6, 98.1%]	2/2 (100.0%) [15.8, 100%]	-	0	82/87 (94.3%) [87.1, 98.1%]
SOF/VEL 24 weeks	65/71 (91.5%) [82.5, 96.8%]	3/4 (75.0%) [19.4, 99.4%]	6/12 (50.0%) [21.1, 78.9%]	2/2 (100.0%) [15.8, 100%]	-	1/1 (100.0%) [2.5, 100%]	77/90 (85.6%) [76.6, 92.1%]

Source: Adapted from Table B-46, p 126 of the submission

Abbreviations: CI = confidence interval; CPT = Child-Pugh-Turcotte; Gt = genotype; SOF/VEL12 = sofosbuvir/velpatasvir FDC for 12 weeks; SOF/VEL24 = sofosbuvir/velpatasvir FDC for 24 weeks; SOF/VEL+RBV12 = sofosbuvir/velpatasvir FDC plus ribavirin for 12 weeks; SVR12 = sustained virological response at 12 weeks following the completion of treatment

Note: Shaded cells represent the recommended regimen in the draft PI document.

- 6.19 ASTRAL-4 had three treatment arms: sofosbuvir/velpatasvir FDC for 12 weeks, sofosbuvir/velpatasvir FDC plus ribavirin for 12 weeks (proposed PBS treatment regimen) and sofosbuvir/velpatasvir FDC for 24 weeks.
- 6.20 The addition of weight-based ribavirin numerically improved SVR12 rates compared to the other treatment arms, despite suboptimal adherence to the ribavirin therapy, particularly among patients with HCV genotype 3. The SVR12 rates achieved by patients with HCV genotype 3 appeared numerically lower than the SVR12 rates for other HCV genotypes across treatment arms. The publication of ASTRAL-4 stated that the small numbers of patients with decompensated cirrhosis and HCV genotype 2, 4, or 6 precluded conclusions about the efficacy of sofosbuvir/velpatasvir FDC among these patients (no patient with HCV genotype 5 enrolled in the study).
- 6.21 Among the patients who received the proposed regimen of sofosbuvir/velpatasvir FDC plus ribavirin, achieved SVR12 and had assessment of hepatic function in ASTRAL-4, 40.7% and 50.6% of patients experienced an improvement in CPT score and Model for End-Stage Liver Disease (MELD) score respectively. Improvements in CPT score were a result of improvements in albumin and bilirubin; whereas improvements in MELD score were from improvements in total bilirubin. Worsening of CPT score was reported in 9.9% of these patients, whereas worsening of MELD score was reported in 34.6% of patients. Longer-term data on liver function and other clinical outcomes (e.g. reversal of liver fibrosis) were not available.

Table 11: Naïve comparison of SVR12 rates in decompensated cirrhosis

Study ID	Study phase	HCV Gt	CPT class	Trans-plant	%treatment experienced ^h	Treatment regimen	Duration (weeks)	SVR12	
								n/N	% (95% CI)
Sofosbuvir/velpatasvir FDC plus ribavirin for 12 weeks									
ASTRAL-4	Phase III	1-4 ^a	CPT B	Pre	54%	SOF/VEL+RBV ^d	12	82/87	94.3% (87.1, 98.1%)
Daclatasvir plus sofosbuvir plus ribavirin for 12 weeks (nominated comparator for HCV Gt 1)									
ALLY-1	Phase III	1-4 ^b	CPT A: 20% ^h CPT B: 53% ^h CPT C: 27% ^h	Pre	60%	DCV+SOF+RBV ^e	12	50/60	83.3% (71.5, 91.7%)
ALLY-1 (Gt 1, CPT B & C)	Phase III	1	CPT B: 71% ^h CPT C: 29% ^h	Pre ^h	NR (mixed)	DCV+SOF+RBV ^e	12	27/34	79.4% (62.1, 91.3%)
UK EAP ^h	Real-world	All	CPT B or C	Pre	NR (mixed)	DCV+SOF+RBV ^f	12	114/150	76.0% (68.4, 82.6%)
UK EAP (Gt 1)	Real-world	1	CPT B or C	Pre ^h	NR (mixed)	DCV+SOF+RBV ^f	12	30/34	88.2% (72.5, 96.7%)
UK EAP (Gt 3) ^h	Real-world	3	CPT B or C	Pre	NR (mixed)	DCV+SOF+RBV ^f	12	75/105	71.4% (61.8, 79.8%)
UK EAP (Other) ^h	Real-world	Other	CPT B or C	Pre	NR (mixed)	DCV+SOF+RBV ^f	12	9/11	81.8% (48.2, 97.7%)
Daclatasvir plus sofosbuvir plus ribavirin for 24 weeks (nominated comparator for HCV Gt 3)									
No data ^h	-	-	-	-	-	DCV+SOF+RBV	24	-	-
Ledipasvir/sofosbuvir plus ribavirin for 12 weeks (concurrent submission for all genotypes)									
SOLAR-1/2	Phase II	1, 4 ^c	CPT B: 67% ^h CPT C: 33% ^h	Pre: 64% ^h Post: 36% ^h	75%	LDV/SOF+RBV ^g	12	131/155	84.5% (77.8, 89.8%)
UK EAP ^h	Real-world	All	CPT B or C	Pre	NR (mixed)	LDV/SOF+RBV ^f	12	194/229	84.7% (79.4, 89.1%)
UK EAP (Gt 1)	Real-world	1	CPT B or C	Pre ^h	NR (mixed)	LDV/SOF+RBV ^f	12	136/149	91.3% (85.5, 95.3%)
UK EAP (Gt 3)	Real-world	3	CPT B or C	Pre ^h	NR (mixed)	LDV/SOF+RBV ^f	12	37/57	64.9% (51.1, 77.1%)
UK EAP (Other)	Real-world	Other	CPT B or C	Pre ^h	NR (mixed)	LDV/SOF+RBV ^f	12	21/23	91.3% (72.0, 98.9%)

Source: Adapted from Tables B-47, p127 and B-53, p139 of the submission; Poordad *et al* (2016); concurrent ledipasvir/sofosbuvir submission

Abbreviations: CI = confidence interval; CPT = Child-Pugh-Turcotte; DCV = daclatasvir; EAP = expanded access program; Gt = genotype; HCV = hepatitis C virus; LDV/SOF = ledipasvir/sofosbuvir; NR = not reported; RBV = ribavirin; SOF = sofosbuvir; SOF/VEL = sofosbuvir/velpatasvir FDC; SVR12 = sustained virological response at 12 weeks following the completion of treatment

Note: Shaded cells represent sofosbuvir/velpatasvir FDC results. 95% CI calculated using Stata14 (binomial exact), during the evaluation.

Footnotes added during the evaluation:

^a The one patient with HCV genotype 6 was not randomised to the sofosbuvir/velpatasvir FDC plus ribavirin arm.

^b 5 patients with HCV genotype 2, 6 patients with HCV genotype 3, and 4 with HCV genotype 4.

^c Only 10 patients had HCV genotype 4

^d Ribavirin 1000 mg/day if <75kg or 1200mg/day if ≥75kg

^e Ribavirin 600 mg/day, with the potential for adjustment to 1000 mg/day based on haemoglobin levels and creatinine clearance.

^f Inclusion and dosage of ribavirin at treating clinician discretion.

^g Ribavirin 600 mg/day, titrate to 1000 mg/day or 1200mg/day if haemoglobin >10.0 g/dL. Can reduce if 600 mg/day not well tolerated.

^h values extracted/added to table during the evaluation

- 6.22 The submission claimed the naïve comparison demonstrated that sofosbuvir/velpatasvir FDC [plus ribavirin] had “higher” SVR12 rates compared to ledipasvir/sofosbuvir FDC with or without ribavirin and daclatasvir plus sofosbuvir with or without ribavirin, where data were available. However, the submission did not include data for regimens without ribavirin. The naïve comparison was at high risk of bias and may not be valid due to the issues raised previously. The claim that sofosbuvir/velpatasvir FDC [plus ribavirin] had “higher” SVR12 rates versus the comparators was inadequately supported given the overlapping 95% CIs across most of the relevant comparisons. Additionally, there was a likely bias in favour of sofosbuvir/velpatasvir FDC plus ribavirin, as the ASTRAL-4 study appeared to have enrolled patients with less severe liver disease versus the comparator studies.
- 6.23 There were very few patients (if any) with decompensated cirrhosis and HCV genotypes 2, 4, 5 and 6 enrolled in the studies included in the naïve comparisons.

Comparative harms

- 6.24 The most commonly reported treatment-emergent adverse events in the sofosbuvir/velpatasvir FDC arms across the key ASTRAL studies were headache, fatigue, nausea, and nasopharyngitis.
- 6.25 There were insufficient patients enrolled in the key studies to detect uncommon adverse events associated with sofosbuvir/velpatasvir FDC. There were limited long term safety data.
- 6.26 The submission did not present comparative data to support the safety claims in the following subgroups:
- comparable safety versus ledipasvir/ sofosbuvir (8, 12 or 24 weeks) in patients with chronic HCV genotype 1 infection, with no cirrhosis or compensated cirrhosis;
 - comparable safety versus daclatasvir plus sofosbuvir for 12 or 24 weeks in patients with chronic HCV genotype 3 infection, with no cirrhosis or compensated cirrhosis;
 - superior safety versus sofosbuvir plus peginterferon plus ribavirin in patients with chronic HCV genotype 4, 5 or 6 infection, with no cirrhosis or compensated cirrhosis; and
 - comparable safety versus daclatasvir plus sofosbuvir for 12 or 24 weeks in patients with decompensated cirrhosis (all HCV genotypes).
- 6.27 Comparative safety data versus active treatment (sofosbuvir plus ribavirin for 12 or 24 weeks) were available from ASTRAL-2 (HCV genotype 2) and ASTRAL-3 (HCV genotype 3) in patients with no cirrhosis or compensated cirrhosis, see Table 12. These trials were limited by the open-label study design, which may bias reporting of adverse events (particularly given the known safety profile of ribavirin). The comparisons for ASTRAL-3 were also confounded by the longer duration of therapy in the sofosbuvir plus ribavirin arm (24 weeks versus 12 weeks) and the likely high risk of bias. No comparative statistics were presented.

Table 12: Summary of key adverse events of ASTRAL-2 and ASTRAL-3; n (%)

	ASTRAL-2 (HCV Gt 2)		ASTRAL-3 (HCV Gt 3)	
	SOF/VEL12 (N=134)	SOF+RBV12 (N=132)	SOF/VEL12 (N=277)	SOF+RBV24 (N=275)
Treatment-emergent AE	92 (68.7)	101 (76.5)	245 (88.4)	260 (94.5)
Grade 3 or 4	3 (2.2)	3 (2.3)	12 (4.3)	23 (8.4)
Treatment-related AE	45 (33.6)	75 (56.8)	170 (61.4)	215 (78.2)
Grade 3 or 4	1 (0.7)	1 (0.8)	3 (1.1)	6 (2.2)
Treatment-emergent SAE	2 (1.5)	2 (1.5)	6 (2.2)	15 (5.5)
Treatment-related SAE	0	0	0	1 (0.4)
AE leading to premature discontinuation of any study drug	1 (0.7)	0	0	9 (3.3)
AE leading to modification or interruption of any study drug	0	13 (9.8)	0	30 (10.9)
Death	2 (1.5)	0	0	3 (1.1)
Treatment-emergent AEs identified in the submission as having a lower frequency in the SOF/VEL12 arm				
Fatigue	20 (14.9)	47 (35.6)	71 (25.6)	105 (38.2)
Headache	24 (17.9)	29 (22.0)	90 (32.5)	89 (32.4)
Nausea	14 (10.4)	19 (14.4)	46 (16.6)	58 (21.1)
Insomnia	6 (4.5)	18 (13.6)	31 (11.2)	74 (26.9)
Anxiety	8 (6.0)	8 (6.1)	7 (2.5)	21 (7.6)
Irritability	4 (3.0)	9 (6.8)	23 (8.3)	40 (14.5)
Pruritus	6 (4.5)	7 (5.3)	8 (2.9)	35 (12.7)
Dyspnoea exertional	1 (0.7)*	3 (2.3)*	3 (1.1)	20 (7.3)
Anaemia	0	8 (6.1)	1 (0.4)	24 (8.7)

Source: Tables B-62 to B-63, pp148-149 and B-66 to B-67 of the submission; *Table 15.11.2.1.2, pp197-207 CSR ASTRAL-2
Abbreviations: AE = adverse event; NR = not reported; SAE = serious adverse event; SOF+RBV12 = sofosbuvir plus ribavirin for 12 weeks; SOF+RBV24 = sofosbuvir plus ribavirin for 24 weeks; SOF/VEL12 = sofosbuvir/velpatasvir FDC for 12 weeks

- 6.28 The submission claimed that treatment with sofosbuvir/velpatasvir FDC compared with sofosbuvir plus ribavirin for 12 or 24 weeks was associated with lower rates of anaemia, insomnia, irritability, anxiety and exertional dyspnoea. Sofosbuvir plus ribavirin also appeared to be associated with higher proportion of patients experiencing fatigue. These events, except anxiety and exertional dyspnoea, were consistent with the adverse events included in the Product Information (PI) document for ribavirin. The claim of higher rates of anxiety and exertional dyspnoea associated with sofosbuvir plus ribavirin for 12 weeks was not evident in ASTRAL-2.
- 6.29 The submission claimed that sofosbuvir/velpatasvir FDC was superior in terms of safety compared to sofosbuvir plus ribavirin for 12 weeks in patient with HCV genotype 2. However, in ASTRAL-2, there were no numerical differences between arms in terms of discontinuation due to adverse events, Grade 3 or 4 adverse events, and serious adverse events.

Clinical claim

Table 13: Summary of the clinical claims made in the submission of sofosbuvir/velpatasvir FDC (12 weeks) versus the nominated comparators across the various subgroups

HCV Gt	Comparator	Clinical claim		Comment from the evaluation
		Efficacy	Safety	
No cirrhosis or compensated cirrhosis				
1	Ledipasvir/sofosbuvir (8, 12 or 24 weeks)	Non-inferior	Comparable	The clinical claims may be reasonable despite not being adequately supported. A naïve comparison for SVR12 was presented, which had major limitations and was at high risk of bias. No comparative safety data were presented.
2	Sofosbuvir + ribavirin (12 weeks)	Superior	Superior	The clinical claim was inadequately supported in terms of comparative efficacy, as although a head-to-head comparison, the 95% CI for SVR12 included differences that were unlikely to be clinically relevant (lower bound of the absolute risk difference was 0.2%). The claim may be reasonable in terms of comparative safety. However, no statistical testing was conducted. Additionally, there did not appear to be numerical differences between arms in terms of discontinuation due to adverse events, Grade 3 or 4 adverse events, and serious adverse events.
3	Daclatasvir + sofosbuvir (12 or 24 weeks)	Non-inferior	Comparable	The clinical claim may be reasonable in terms of daclatasvir + sofosbuvir for 12 weeks in patients with no cirrhosis despite not being adequately supported. A naïve comparison for SVR12 was presented, which had major limitations and was at high risk of bias. No comparative safety data were presented. The submission did not present any comparative data versus daclatasvir + sofosbuvir for <u>24 weeks</u> , the nominated comparator for patients compensated cirrhosis. Thus, the clinical claim versus daclatasvir + sofosbuvir for <u>24 weeks</u> was not supported and is not reasonable.
4-6	Sofosbuvir + peg-IFN + ribavirin (12 weeks)	Superior	Superior	The claim in terms of comparative efficacy was inadequately supported, as there were no differences in SVR12 rates based on a naïve comparison with sparse comparator data. The naïve comparison was at high risk of bias and had major limitations. The safety claim may be reasonable given the known safety profile of peg-IFN, despite not being adequately supported. No comparative safety data were presented.
Decompensated cirrhosis				
1-6	Daclatasvir + sofosbuvir (12 or 24 weeks)	Non-inferior	Comparable	The claim may be reasonable for HCV genotype 1 (daclatasvir + sofosbuvir + ribavirin for 12 weeks) despite not being adequately supported. A naïve comparison for SVR12 were presented, which had major limitations and was at high risk of bias. No comparative safety data were presented. The clinical claims may not be adequately supported for the other HCV genotypes. The submission did not present any comparative data versus daclatasvir + sofosbuvir + ribavirin for <u>24 weeks</u> , the nominated comparator for HCV genotype 3. There were few patients with HCV genotype 2 (n=4) or 4 (n=2), and no patient with HCV genotype 5 or 6 who received sofosbuvir/velpatasvir FDC + ribavirin.

Source: Adapted from pp171-172 of the submission

Abbreviations: FDC = fixed dose combination; Gt = genotype; HCV = hepatitis C virus; peg-IFN = peginterferon alfa-2a; SVR12 = sustained virological response at 12 weeks following the completion of treatment

6.30 The PBAC considered that the claim of non-inferior comparative effectiveness and comparable safety against the nominated comparators was reasonable for

sofosbuvir/velpatasvir FDC treatment in patients with genotypes 1 and 3 (no cirrhosis or compensated cirrhosis). The PBAC also considered a conclusion of non-inferior effectiveness and comparable safety for sofosbuvir/velpatasvir FDC (12 weeks) versus sofosbuvir plus ribavirin (24 weeks) in GT3 was reasonable.

- 6.31 However, for patients with genotypes 2, 4-6, the PBAC viewed the claims of superior comparative effectiveness against the nominated comparators as inadequately supported by the data. In terms of comparative safety for genotype 2, the PBAC considered that the claim of superiority to sofosbuvir plus ribavirin was inadequately supported. For genotypes 4 to 6, while no comparative safety data were presented, the PBAC considered that it may be reasonable to conclude that sofosbuvir/velpatasvir FDC would be superior in safety to sofosbuvir+peg-IFN+ribavirin, given the well-known limitations of interferon-containing regimens.
- 6.32 For patients with decompensated cirrhosis, the PBAC considered that a claim of non-inferior comparative effectiveness and comparable safety with daclatasvir+sofosbuvir+/-ribavirin may be reasonable despite not being adequately supported.
- 6.33 The PBAC noted that a number of other potential comparators exist, and that sofosbuvir/velpatasvir FDC had not demonstrated superior comparative effectiveness or comparative safety over any alternative regimens.

Economic analysis

- 6.34 The submission presented a cost-minimisation analysis based on published prices.

The PBAC noted that the department would need to conduct an alternative cost-minimisation analysis on the basis of the effective prices for the regimens included in the *General Statement*, compared with the regimen approved by the TGA for sofosbuvir/velpatasvir FDC.

Drug cost/patient/course:

Table 14: Drug cost/patient/course at published prices (3 scripts per item per patient per course)

Treatment regimen	Drug cost/patient/course
Sofosbuvir 400mg/ velpatasvir 100mg daily for 12 weeks	\$ [REDACTED]
Sofosbuvir 400mg/ velpatasvir 100mg daily plus ribavirin 600 mg/day for 12 weeks	\$ [REDACTED]
Sofosbuvir 400mg/ velpatasvir 100mg daily plus ribavirin 1000 mg/day for 12 weeks ^a	\$ [REDACTED]
Sofosbuvir 400mg/ velpatasvir 100mg daily plus ribavirin 1200 mg/day for 12 weeks ^a	\$ [REDACTED]

Source: 'Epclusa PBAC Submission Section E Workbook.xlsx'

Note: Assumed General Schedule = 80.83%, S100 (Public hospital) = 18.61% and S100 (Private hospital) = 0.56%

^a added during the evaluation

- 6.35 As the sponsor is willing to discuss potential Special Pricing Arrangements, these prices do not represent the effective prices.

Estimated PBS usage & financial implications

- 6.36 This submission was not considered by DUSC. The submission used a mixed epidemiological and market share approach. The numbers of treated patients with chronic HCV infection were sourced from the Deed of Agreement 2016, with

assumed varying market uptake by treatment regimen and HCV genotype from the estimated current market composition (which was mostly informed by PBS utilisation data between March 2016 and May 2016). The sponsor stated that the presented financial implications based on published prices were only illustrative, as currently listed HCV treatments are subject to Special Pricing Arrangements. The redacted table below shows that at year 5 the estimated number of patients was less than 10,000 per year and the net save to the PBS would be more than \$100 million per year.

Table 15: Estimated use and financial implications at published prices

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Patients treated with SOF/VEL ^a					
No cirrhosis or compensated cirrhosis (uptake: %)					
Decompensated cirrhosis (uptake: %)					
SOF/VEL scripts (3 scripts/pt)					
Cost of SOF/VEL (DPMQ less co-payment)	\$	\$	\$	\$	\$
Estimation of changes in use and cost of other drugs					
Net cost from change in use of other drugs	-\$	-\$	-\$	-\$	-\$
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	-\$	-\$	-\$	-\$	-\$
Net cost to MBS	-\$	-\$	-\$	-\$	-\$
Estimated total net cost					
Net cost to PBS/RPBS/MBS	-\$	-\$	-\$	-\$	-\$

Source: 'Epcclusa PBAC Submission Section E Workbook.xlsx'

Abbreviations: DPMQ = dispensed price for maximum quantity; pt = patient; SOF = sofosbuvir; VEL = velpatasvir

^a Values in the submission were not rounded to a whole patient; which resulted in inaccurate estimates. These were corrected during the evaluation.

- 6.37 The PBAC noted the Department would need to recalculate the financial estimates on the basis of the effective prices for the regimens included in the *General Statement*, compared with the price agreed for the sofosbuvir/velpatasvir FDC. The PBAC agreed that the claimed MBS cost-offsets based on a reduction in HCV genotype testing and an initial consultation with a specialist were unlikely to be achieved; as it was unlikely that all patients with no cirrhosis or compensated cirrhosis treated with sofosbuvir/velpatasvir FDC would not have a HCV genotype test.

Quality Use of Medicines

- 6.38 The submission claimed that the availability of sofosbuvir/velpatasvir FDC provides a simplified regimen; requiring one tablet once daily for 12 weeks regardless of HCV genotype, prior treatment experience and cirrhosis status (with the addition of ribavirin in patients with decompensated cirrhosis). The submission claimed sofosbuvir/velpatasvir FDC would remove the potential for prescriber confusion (particularly in the primary care setting), and treatment outcomes would not be compromised by difficulties in assessing intermediate stages of liver fibrosis and inaccuracies in HCV genotyping. The extent of the claimed reduction in prescribing errors and compromised patient care were unclear.

- 6.39 The submission claimed that the availability of sofosbuvir/velpatasvir FDC would increase equitable access to HCV treatments in the following scenarios:
- Rural and remote settings: The submission claimed that sofosbuvir/velpatasvir FDC will facilitate access in the community and general practice settings, thus improving equity for all patients.
 - Access to interferon-free and ribavirin-free regimens: The currently PBS-listed treatment regimen for patients with HCV genotype 2 is sofosbuvir plus ribavirin and genotypes 4-6 is sofosbuvir plus peginterferon plus ribavirin. The submission argued that PBS-listing of sofosbuvir/velpatasvir FDC for these genotypes would ensure equitable access to regimens without ribavirin or peginterferon. However, ribavirin is still required for patients with decompensated cirrhosis.
 - Custodial settings: However, uptake in this setting is likely to be affected by factors external to the dosing regimen.

Financial Management – Risk Sharing Arrangements

- 6.40 The PBAC recommended that sofosbuvir/velpatasvir FDC enter the Risk Sharing Arrangement (RSA) currently in place for other drugs used for the treatment of CHC, and be subject to the same Subsidisation Caps and rebate arrangements.

7 PBAC Outcome

- 7.1 The PBAC recommended the Authority Required General Schedule and Section 100 listing of sofosbuvir with velpatasvir for the treatment of chronic hepatitis C infection for patients with genotypes 1-6 and no cirrhosis. The PBAC also recommended the Authority Required General Schedule and Section 100 listing of sofosbuvir with velpatasvir +/- ribavirin for the treatment of chronic hepatitis C infection for patients with genotypes 1-6 and cirrhosis.
- 7.2 The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of sofosbuvir with velpatasvir +/- ribavirin would be acceptable if it were cost-minimised against the relevant lowest priced alternative regimen in the *General Statement*.
- 7.3 The PBAC considered that the PBS restriction should be consistent with other drugs listed in the *General Statement for Drugs for the Treatment of Hepatitis C*, and recommended that the maximum quantity should provide for one pack, and two repeats, allowing for 12 weeks' treatment duration. The PBAC also noted that the final restriction will be based on the TGA registration. The PBAC further advised that it was unnecessary for the *General Statement* to differentiate between regimens suitable for patients with compensated versus decompensated cirrhosis, as proposed by the submission. The PBAC noted that the *General Statement* criteria restrict prescribing to medical practitioners experienced in the treatment of hepatitis C, and that prescribers are required to treat their patients in line with both the PBS criteria and the TGA Product Information. The PBAC considered that the requirement to add ribavirin to sofosbuvir/velpatasvir in patients with decompensated cirrhosis could be dealt with in the existing format of the *General Statement*.

- 7.4 The PBAC viewed that the availability of this regimen will likely have a considerable impact on prescribing choices for HCV treatment in Australia, as it is anticipated that there is likely to be a prescriber preference for a regimen that can act against all genotypes.
- 7.5 The PBAC considered that the clinical evaluation presented by the submission – based on four key Phase III trials and one supplementary single-arm study, and a series of naïve comparisons – allowed the PBAC to reasonably conclude non-inferior comparative efficacy and safety to the nominated comparators, despite not all claims being well supported. The PBAC also considered a conclusion of non-inferior effectiveness and comparable safety for sofosbuvir/velpatasvir FDC (12 weeks) versus sofosbuvir plus ribavirin (24 weeks) in GT3 was reasonable.
- 7.6 The exception was that the PBAC did consider it reasonable to conclude that sofosbuvir with velpatasvir would be superior in safety to sofosbuvir+peg-IFN+ribavirin for treatment of genotypes 4-6, given the well-known limitations of interferon-containing regimens. The PBAC considered that the data did not adequately support a claim of superior efficacy in comparison with this regimen. Nor did the data presented support the claims that sofosbuvir with velpatasvir demonstrated superior efficacy and safety compared with sofosbuvir plus ribavirin for the treatment of genotype 2.
- 7.7 The PBAC noted that in the absence of demonstrated superior comparative effectiveness or comparative safety of sofosbuvir with velpatasvir over alternative regimens, there is no basis for sofosbuvir with velpatasvir to have a cost advantage over the lowest priced regimen.
- 7.8 Overall, the PBAC viewed that sofosbuvir with velpatasvir treatment showed high SVR12 response rates irrespective of genotype and cirrhosis status. Although patients with GT3 CHC, and particularly those with GT3 and decompensated cirrhosis, showed lower response rates compared to other patient types, these were still considered acceptable by the PBAC, given that it is well acknowledged that these groups are among the most difficult to treat.
- 7.9 The PBAC recommended that, under s101(3BA) of the *National Health Act 1953*, sofosbuvir with velpatasvir should be treated as interchangeable on an individual patient basis with:
- Ledipasvir with sofosbuvir, and with paritaprevir with ritonavir with ombitasvir and dasabuvir +/- RBV, for genotype 1 (recalling its July 2016 advice under s101(3BA)).
 - Sofosbuvir in combination with ribavirin, for genotypes 2 and 3.
 - Daclatazvir and sofosbuvir, for genotype 3.
 - Grazoprevir with elbasvir +/- RBV, for genotype 4.
- 7.10 The PBAC also recommended that sofosbuvir with velpatasvir enter the RSA currently in place for other drugs used for the treatment of CHC, and be subject to the same Subsidisation Caps and rebate arrangements.
- 7.11 The PBAC advised that sofosbuvir with velpatasvir should have the same nurse practitioner prescribing arrangements as other HCV treatments under the *General*

Statement.

- 7.12 The PBAC recommended that the Early Supply Rule should apply to the listing of sofosbuvir with velpatasvir under the General Schedule.
- 7.13 The PBAC noted that this submission was not eligible for an Independent Review because it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty (units)	Max. Qty (packs)	No. of Rpts	Proprietary Name and Manufacturer	
SOFOSBUVIR + VELPATASVIR Sofosbuvir 400 mg + velpatasvir 100 mg tablet	28	1	2	Eplusa®	Gilead Sciences Pty Ltd
Category / Program:	GENERAL – General Schedule (Code GE) Section 100 – Highly Specialised Drugs Program				
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners				
PBS Indication:	Chronic hepatitis C infection				
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone				
Clinical criteria:	Patient must meet the criteria set out in the General Statement for Drugs for the Treatment of Hepatitis C, AND Patient must be taking this drug as part of a regimen set out in the matrix in the General Statement for Drugs for the Treatment of Hepatitis C, based on the hepatitis C virus genotype, patient treatment history and cirrhotic status, AND The treatment must be limited to a maximum duration of 12 weeks.				
Administrative Advice	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.				

The additions to the *General Statement for Drugs for the Treatment of Hepatitis C* will be based on the TGA registration.

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 welcomes the positive PBAC recommendation and looks forward to working with the Department to make Eplusa available to Australian patients as soon as possible. The Sponsor notes that in point 7.8 the PBAC has specified (pursuant to s101(3BA)) that Eplusa should be treated as interchangeable with particular other drugs. The issue of interchangeability with those other drugs was not addressed in the Sponsor's submission and importantly there are groups of patients who, by the virtue of specific characteristics (other than genotype) cannot be treated

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with all the drugs determined to be interchangeable. The Sponsor wishes to understand the basis of the PBAC's decision and welcomes discussing this further with the Department as part of the post-PBAC process and, where appropriate, providing the PBAC with information relevant to interchangeability.