

## 5.11 SOFOSBUVIR with VELPATASVIR and VOXILAPREVIR, 400mg/100mg/100mg tablets, VOSEVI<sup>®</sup>, Gilead Sciences Pty Limited.

### 1 Purpose of Application

- 1.1 The submission requested Section 100 and Section 85 listing for sofosbuvir with velpatasvir and voxilaprevir for treatment of adult patients with chronic hepatitis C (CHC) who have received prior treatment with an NS5A-based treatment regimen and not achieved sustained virological response (SVR). Sofosbuvir with velpatasvir and voxilaprevir has not been previously considered by the PBAC.
- 1.2 The requested basis for listing was cost-effectiveness compared to standard medical management (no active treatment).
- 1.3 The key components of the clinical issue addressed by the submission is presented in Table 1.

**Table 1: Key components of the clinical issue addressed by the submission**

Component	Description
Population	Hepatitis C-infected patients who have failed to achieve virological response with non-structural protein 5A (NS5A) therapy
Intervention	Sofosbuvir + velpatasvir + voxilaprevir
Comparator	Standard medical management (supportive care only, no active treatment); this is reasonable, however upon PBS-listing of glecaprevir with pibrentasvir (recommended for listing in patients infected with chronic hepatitis C (CHC) that have failed prior treatment with the use of an NS5A inhibitor at the November 2017 PBAC meeting), glecaprevir with pibrentasvir would become the appropriate comparator.
Outcomes	Sustained virological response at 12 weeks
Clinical claim	Sofosbuvir + velpatasvir + voxilaprevir is superior to no active treatment

NS5A = non-structural protein 5A

Source: Table 1.1, p15 of the submission.

## 2 Requested listing

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
SOFOSBUVIR + VELPATASVIR & VOXILAPREVIR 400mg/100mg/100mg tablet	1	28	2	\$85	VOSEVI ®, Gilead Sciences Pty Limited
				\$ [redacted] published price	
				\$ [redacted] effective price	
				\$100 Private	
				\$ [redacted] published price	
				\$ [redacted] effective price	
				\$100 Public	
				\$ [redacted] published price	
				\$ [redacted] effective price	
<b>Category</b>	Section 100 and Section 85				
<b>Condition:</b>	Chronic Hepatitis C				
<b>PBS Indication:</b>	Hepatitis C-infected patients who have failed to achieve virological response with non-structural protein 5A (NS5A) therapy				
<b>Treatment phase:</b>	Initial				
<b>Restriction:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined				
<b>Treatment criteria:</b>	Patient must have received prior treatment with a NS5A-based treatment regimen and not achieved sustained virological response.				
<b>Population criteria:</b>	Patient must be adult.				

Source: Table 1.3, p17, and p28 of the submission.

- 2.1 The submission stated that in accordance with currently listed therapies for CHC, it was requested that sofosbuvir with velpatasvir and voxilaprevir be subject to a Special Pricing Arrangement (SPA).
- 2.2 The submission proposed that the existing CHC treatment matrix in the General Statement for Drugs for the Treatment of Hepatitis C be modified to create a separate ‘treatment experienced’ category for patients that have failed treatment with NS5A-based treatment regimen (see table 2 below).
- 2.3 The ESC noted that the General Statement for Drugs for the Treatment of Hepatitis C (the General Statement) currently specifies treatments according to prior treatment experience (where treatment-experienced refers to prior exposure to peg-interferon) and cirrhotic status. The ESC further noted that as glecaprevir with pibrentasvir has been recommended for listing and sofosbuvir with velpatasvir and voxilaprevir is now requesting listing specifically in patients who have failed prior NS5A therapy, the PBAC may wish to consider whether the General Statement should be amended or changed to reflect specific use of these therapies in these patients. This will become particularly relevant should sofosbuvir with velpatasvir

and voxilaprevir be PBS-listed among only patients who are NS5A treatment-experienced to avoid any potential use of sofosbuvir with velpatasvir and voxilaprevir as a first-line DAA (there are two randomised trials assessing the use of this regimen among DAA-naïve patients, POLARIS-2 and -3).

- 2.4 In addition to patients who were NS5A-experienced, the European Medicines Agency (EMA) approved sofosbuvir with velpatasvir and voxilaprevir in patients who were direct acting antiviral (DAA) naïve based on results of the POLARIS-2 and POLARIS-3 studies. It is therefore likely that sofosbuvir with velpatasvir and voxilaprevir could be used beyond the requested restriction of only NS5A experienced patients. Given that the NS5A experienced population is a fraction of the size of the NS5A naïve population, treatment outside of the restriction could be considerable. The Pre-Sub-Committee Response (PSCR) stated that usage outside the requested restriction is likely to be minimal due to the proposed restriction wording and possible changes to the treatment matrix. In addition, the sponsor noted that if recommended for listing, sofosbuvir with velpatasvir and voxilaprevir would likely join the existing Risk Sharing Arrangement (RSA) for other drugs for the treatment of HCV – as per the glecaprevir with pibrentasvir recommendation.

**Table 2: Proposed modified PBS treatment matrix**

GT	Treatment naïve	Treatment experienced	
		Non-NS5A failures	NS5A failures
1	SOFOSBUVIR + VELPATASVIR (EPCLUSA)	SOFOSBUVIR + VELPATASVIR (EPCLUSA)	SOFOSBUVIR + VELPATASVIR + VOXILAPREVIR (VOSEVI)
	LEDIPASVIR + SOFOSBUVIR (HARVONI)	LEDIPASVIR + SOFOSBUVIR (HARVONI)	
	DACLATASVIR + SOFOSBUVIR PARITEPRASIR + RITONAVIR + OMBITASVIR & DASABUVIR (Viekira Pak)	DACLATASVIR + SOFOSBUVIR PARITEPRASIR + RITONAVIR + OMBITASVIR + DASABUVIR (Viekira Pak)	
	PARITEPRASIR + RITONAVIR + OMBITASVIR & DASABUVIR & RIBAVIRIN (Viekira Pak RBV)	PARITEPRASIR + RITONAVIR + OMBITASVIR & DASABUVIR + RIBAVIRIN (Viekira Pak RBV)	
	GRAZOPREVIR + ELBASVIR (Zepatier)	GRAZOPREVIR + ELBASVIR (Zepatier) ± RIBAVIRIN	
	SOFOSBUVIR & PEGYLATED INTERFERON & RIBAVIRIN	SOFOSBUVIR & PEGYLATED INTERFERON & RIBAVIRIN	
2	SOFOSBUVIR + VELPATASVIR (EPCLUSA)	SOFOSBUVIR + VELPATASVIR (EPCLUSA)	SOFOSBUVIR + VELPATASVIR + VOXILAPREVIR (VOSEVI)

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	SOFOSBUVIR + RIBAVIRIN	SOFOSBUVIR + RIBAVIRIN	
<b>3</b>	SOFOSBUVIR + VELPATASVIR (EPCLUSA) DACLATASVIR + SOFOSBUVIR SOFOSBUVIR + RIBAVIRIN SOFOSBUVIR & PEGYLATED INTERFERON & RIBAVIRIN	SOFOSBUVIR + VELPATASVIR (EPCLUSA) DACLATASVIR + SOFOSBUVIR SOFOSBUVIR + RIBAVIRIN SOFOSBUVIR & PEGYLATED INTERFERON & RIBAVIRIN	SOFOSBUVIR + VELPATASVIR + VOXILAPREVIR (VOSEVI)
<b>4</b>	SOFOSBUVIR + VELPATASVIR (EPCLUSA) GRAZOPREVIR + ELBASVIR (Zepatier) SOFOSBUVIR & PEGYLATED INTERFERON & RIBAVIRIN	SOFOSBUVIR + VELPATASVIR (EPCLUSA) GRAZOPREVIR + ELBASVIR (Zepatier) ± RIBAVIRIN SOFOSBUVIR & PEGYLATED INTERFERON & RIBAVIRIN	SOFOSBUVIR + VELPATASVIR + VOXILAPREVIR (VOSEVI)
<b>5&amp;6</b>	SOFOSBUVIR + VELPATASVIR (EPCLUSA) SOFOSBUVIR & PEGYLATED INTERFERON & RIBAVIRIN	SOFOSBUVIR + VELPATASVIR (EPCLUSA) SOFOSBUVIR & PEGYLATED INTERFERON & RIBAVIRIN	SOFOSBUVIR + VELPATASVIR + VOXILAPREVIR (VOSEVI)

Source: p24 of the submission

### 3 Background

#### **Registration status**

- 3.1 The submission was made under TGA/PBAC Parallel Process. At the time of PBAC consideration, the clinical evaluation report and TGA delegate's overview were available. The delegate indicated that at this time they have no reason to say that the application for sofosbuvir with velpatasvir and voxilaprevir should not be approved. Registration is expected on 30 April 2018.
- 3.2 The PBAC has not previously considered sofosbuvir with velpatasvir and voxilaprevir.

### 4 Population and disease

- 4.1 Chronic hepatitis C (CHC) is a blood borne inflammatory liver disease caused by the hepatitis C virus (HCV). Untreated chronic infection may lead to cirrhosis, liver failure, hepatocellular carcinoma and death. In Australia, CHC is treated with combination treatments that include inhibitors of the non-structural protein 5A (NS5A).
- 4.2 According to the observational study REACH C (Kirby Institute 2017) NS5A therapies led to sustained virological response (i.e. cure) in 95-97% of Australian patients. Consequently, 3-5% of patients may fail to achieve virological response after NS5A treatment. These patients tend to have more advanced disease, and have a higher occurrence of cirrhosis, than the general CHC population.
- 4.3 Sofosbuvir with velpatasvir and voxilaprevir would be prescribed after NS5A treatment failure (also referred to as NS5A treatment experienced). Sofosbuvir with velpatasvir and voxilaprevir is a single fixed dose combination tablet containing:
  - 400mg sofosbuvir (pan-genotypic inhibitor of HCV NS5B RNA-dependent RNA polymerase, an essential enzyme for viral replication);
  - 100mg velpatasvir (pan-genotypic HCV inhibitor targeting the HCV NS5A protein, which is essential for HCV NRA replication and assembly of HCV virions); and
  - 100mg voxilaprevir (pan-genotypic inhibitor of the NS3/4A protease, acts as a noncovalent reversible inhibitor).

### 5 Comparator

- 5.1 The submission nominated standard medical management (supportive care only, no active treatment) as the main comparator. This was reasonable.
- 5.2 The PBAC recommended the Authority Required General Schedule and Section 100 listing of glecaprevir with pibrentasvir for the treatment of chronic hepatitis C infection for treatment naïve and treatment experienced patients (including those with prior NS5A treatment) with genotypes 1-6, with or without cirrhosis in November 2017, (Glecaprevir with pibrentasvir, PBAC web outcome; November

2017). The ESC agreed that upon PBS listing of glecaprevir with pibrentasvir, this treatment regimen would be the appropriate comparator for sofosbuvir with velpatasvir and voxilaprevir.

- 5.3 The Pre-Sub-Committee Response (PSCR) agreed that upon PBS listing glecaprevir with pibrentasvir would become the appropriate comparator for patients with genotype 1 HCV – in line with its approved TGA indication. However, the sponsor considered that until details of the glecaprevir with pibrentasvir recommendation and proposed listing are known, that standard medical management may remain the appropriate comparator for genotypes 2-6. The pre-PBAC response maintained that glecaprevir with pibrentasvir is only an appropriate comparator in NS5A failures with GT1 CHC, who have not previously been treated with an NS5A + Protease Inhibitor (PI) regimen, given that the TGA has only approved its use in patients with GT1 CHC who were previously treated with either a regimen of an NS5A inhibitor or with an NS3/4A protease inhibitor, but not both classes of inhibitors.
- 5.4 Although the submission nominated no treatment as the comparator, citing the lack of currently available treatments for patients who have failed treatment with an NS5A inhibitor; it should be noted that retreatment of patients that have failed prior treatment with the use of an NS5A inhibitor with currently PBS-listed regimens is possible and likely as:
- the General Statement for Drugs for the Treatment of Hepatitis C does not preclude such use. Amendments to the General Statement may be warranted;
  - although the Australian recommendations for the management of hepatitis C virus infection: a consensus statement (August 2017) state that “Retreatment with the same treatment regimen is not recommended”, there are numerous regimens to choose from; and
  - a survey of 14 physicians, conducted on behalf of the sponsor, indicated that a significant proportion of patients are currently being retreated.

The pre-PBAC response maintained that the General Statement be amended to clearly distinguish between regimens approved for use in patients who have failed treatment with an NS5A inhibitor and those who have failed treatment with non-NS5A therapy. The sponsor argued that this would align current treatment guidelines with international guidelines and prevent the use of sofosbuvir with velpatasvir and voxilaprevir as a first-line treatment.

## **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 organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with sofosbuvir with velpatasvir and voxilaprevir including the addition of a pan-genotypic treatment option for patients with HCV, particularly in patients who have previously failed treatment with NS5A-based direct acting antiviral treatment regimen, as well as the high SVR rates achieved in patients without cirrhosis or with compensated cirrhosis. The input from Hepatitis Australia also noted that allowing streamlined access to sofosbuvir with velpatasvir and voxilaprevir and ensuring its inclusion on both the General Schedule (S85) and S100 Schedule would ensure patients who wish to access the medication outside of the hospital setting, would be able to do so via their general practitioner or nurse practitioner.

### ***Clinical trials***

6.3 The submission was based on one head-to-head randomised trial comparing sofosbuvir with velpatasvir and voxilaprevir to placebo (POLARIS-1; n=416). Two Phase 2 open-label studies, (GS-US-367-1168 and TRILOGY-3) were identified in the Sponsor's database and the TGA dossier, and were included in a supplementary appendix to the submission.

6.4 The submission also included discussion of the glecaprevir with pibrentasvir trial MAGELLAN-1 in reference to a naïve comparison presented in an Appendix. MAGELLAN-1 (Part 2) (n=91) was a randomised open label trial comparing glecaprevir with pibrentasvir for 12 weeks to glecaprevir with pibrentasvir for 16 weeks in patients with CHC genotype 1 or 4 with prior NS5A treatment failure.

6.5 Details of the trials presented in the submission are provided in Table 3.

**Table 3: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Included trials - sofosbuvir + velpatasvir + voxilaprevir</b>		
POLARIS-1 GS-US-367- 1171	(POLARIS 1 CSR) A Phase 3, Global Multicenter, Randomised Double-Blind, Placebo-Controlled Study to Investigate the Safety and Efficacy of Sofosbuvir/Velpatasvir/GS-9857 Fixed-Dose Combination for 12 Weeks in Direct-Acting Antiviral-Experienced Subjects with Chronic HCV Infection.	2016.
	Bourlière M, Gordon SC, Flamm SL, Cooper CL, Ramji A, Tong M, Ravendhran N, Vierling JM, et al. Sofosbuvir, velpatasvir, and voxilaprevir for previously treated HCV infection.  Bourlière M, Gordon SC, Ramji A, Ravendhran N, Tran TT, Hynad RH, et al. Sofosbuvir/ Velpatasvir/ Voxilaprevir for 12 Weeks as a Salvage Regimen in NS5A inhibitor-Experienced Patients with Genotype 1-6 Infection: The Phase 3 Polaris 1 Study	<i>NEJM</i> 2017; 376(22): 2134-2136  <i>Hepatology</i> 2016; 63 (1S: 102A [Abstract])
TRILOGY-3 GS-US-367- 1871	A Phase 2, Open Label Study to investigate the Safety and Efficacy of Sofosbuvir/GS5816/GS9857 Fixed-Dose Combination with or without Ribavirin in Subjects with Chronic Genotype 1 HCV. Infection Previously Treated with a Direct Acting Antiviral Regimen.	August 2016
	Lawitz E, Poordad F, Wells J, Hyland RH, Yang Y, Dvory-Sobol H. Sofosbuvir-velpatasvir-voxilaprevir with or without ribavirin in direct-acting antiviral-experienced patients with genotype 1 hepatitis C virus	<i>Hepatology</i> 2017; 65 (6): 1803-1809
	Lawitz E, Kowdley K, Curry M, Reau N, Nguyen M, Kwo P. High efficacy of sofosbuvir/velpatasvir plus GS-9857 for 12 weeks in treatment-experienced genotype 1-6 HCV-infected patients, including those previously treated with direct-acting antivirals.	<i>Am Jml Gastr Conf:</i> 2016; 111: S380
GS-US-367- 1168	Lawitz E, Poordad F, Wells J, Hyland RH, Yany Y, Dvory-SObol H, Stamm LM, Brainard DM, McHutchinson, JG, Landaverde C, Gutierrez J. High Efficacy of Sofosbuvir/Velpatasvir/GS9857 With or Without Ribavirin for 12 Weeks in Direct Acting Antiviral-Experienced	<i>J Hepatol</i> 2016; 64: S146 [presentation]
	A Phase 2, Global Multicenter, Open-Label Study to Investigate the Safety and Efficacy of GS-9857 plus Sofosbuvir/GS-5816 Fixed Dose Combination in Subjects with Chronic Genotype 1 HCV Infection.	No date Provided
MAGELLAN- 1 (Part 2)	Lawitz E, Kowdley K, Curry M, Reau N, Nguyen M, Kwo P, et al. High Efficacy of Sofosbuvir/Velpatasvir Plus GS-9857 for 12 Weeks in Treatment-Experienced Genotype 1-6 HCV-Infected Patients, Including Those Previously Treated With Direct-Acting Antivirals.	<i>EASL 2016</i> [Presentation]
	Poordad F., Pol S, Asatryan A, Buti M, Shaw D, Hézode C, et al., MAGELLAN-1, Part 2: glecaprevir and pibrentasvir for 12 or 16 weeks in patients with chronic hepatitis C virus genotype 1 or 4 and prior direct-acting antiviral treatment failure	<i>J Hepatol</i> 2017; 66 (1 suppl) S83-84
	Poordad F., Pol S, Asatryan A, Buti M, Shaw D, Hézode C, et al., MAGELLAN-1, Part 2: glecaprevir and pibrentasvir for 12 or 16 weeks in patients with chronic hepatitis C virus genotype 1 or 4 and prior direct-acting antiviral treatment failure.  Poordad F, Felizarta F, Asatryan A, Sulkowski MS, Reindollar RW, Landis CS, et al., Glecaprevir and pibrentasvir for 12 weeks for hepatitis C virus genotype 1 infection and prior direct-acting antiviral treatment.	<i>Gastroenterology</i> , 2017; 152 (5) suppl 1 pS1057.  <i>Hepatology</i> 2017; 66(2):389-397.

Source: Table 2.4, p37 of the submission, Table 1, p3 of Appendix 3 to the submission and the Section 2 annotated literature search in Attachment to the submission

6.6 The key features of the direct randomised trials are summarised in Table 4.

**Table 4: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
<b>Sof+vel+vox vs placebo</b>						
POLARIS-1	416	R, DB	Low	NS5A treated	SVR12	SVR12
<b>GP 12 weeks versus GP 16 weeks</b>						
MAGELLAN-1 (Part 2)	91	R, OL	Unclear	DAA treated patients, GT 1, 4	SVR	Not applicable

DB=double blind; GP = glecaprevir with pibrentasvir; Gt = genotype; OL=open label;; R=randomised; sof+vel+vox = sofosbuvir, velpatasvir and voxilaprevir

Source: Section 2.3 p39-42 of the submission, and appendix 3 to the submission.

6.7 Little publically available information was found on the MAGELLAN-1 (Part 2) trial. Due to this lack of information, it was difficult to describe the risk of bias.

6.8 MAGELLAN-1 (Part 2) only included SVR data for genotypes 1 and 4, while POLARIS 1 included data for all genotypes. The ESC noted that of the 416 patients in POLARIS 1 only 300, all of which had genotype 1, were included in the RCT population (150 in each arm). The remaining 116 patients, mostly those with genotype 3, were not randomised with all patients receiving sofosbuvir with velpatasvir and voxilaprevir.

6.9 POLARIS-1 had a more narrowly defined population of NS5A-experienced patients rather than DAA-experienced patients.

### **Comparative effectiveness**

6.10 The key results of sustained virological response for POLARIS-1 are presented in Table 5.

6.11 The TGA evaluator stated that there was ‘overwhelming evidence for efficacy of proposed FDC of SOF/VEL/VOX... in patients with prior exposure to NS5A inhibitor DAA treatment with consistent efficacy observed across all genotypes of HCV and irrespective of cirrhotic status of patients’.

6.12 The TGA evaluator also noted that results presented in the CSR were only interim results and the 24 weeks post treatment data was still pending. TGA-adopted CHMP guidelines state that the recommended primary endpoint for confirmatory studies is SVR defined as undetectable HCV RNA 6 months after completion of therapy, regardless of scheduled duration of treatment. Consequently, the evaluator considered that in order to confirm the evidence of efficacy in this patient population, “it is imperative that the SVR24 results should be submitted when available” . The same interim results were presented in the submission.

**Table 5: Results of SVR12 outcomes in the POLARIS-1 trial**

Trial ID	Sof+vel+vox n/N (%)	CI	Placebo
SVR12			
All Genotypes	253/263 (96.2)	93.1, 98.2	0
Genotype 1	146/150 (97.3)	93.3, 99.3	0
1a	97/101 (96.0)	90.2, 98.9	NA
1b	45/45 (100.0)	92.1, 100.0	
1 other	4/4 (100.0)	39.8, 100.0	
2	5/5 (100.0)	47.8, 100.0	
3	74/78 (94.9)	87.4, 98.6	
4	20/22 (90.9)	70.8, 98.9	
5	1/1 (100.0)	2.5, 100.0	
6	6/6 (100.0)	54.1, 100.0	
unknown	1/1 (100.0)	2.5, 100.0	
Cirrhosis	113/121 (93.4)	87.4, 97.1	0
No Cirrhosis	140/142 (98.6)	95.0, 99.8	0
Treatment experienced	253/263 (96.2%)	93.1, 98.2	0
DAA-Experienced	253/263 (96.2%)	93.1, 98.2	0
NS5A±DAA	252/262 (96.2%)	93.1, 98.2	0
NS5A+NS5B	151/161 (93.8%)	88.9, 97.0	0
NS5A+NS3±NS5B	83/83 (100.0%)	95.7, 100.0	0
NS5A±Other(s)	18/18 (100.0%)	81.5, 100.0	0
Other(s)	1/1 (100.0%)	2.5, 100.0	0

CI = confidence interval; DAA = direct acting anti-viral; n = number of participants with event; N = total participants in group; NA = not applicable; NS4 = non-structural protein; SVR = sustained virologic response

Source: Table 2.15, p 56-57 of the submission.

- 6.13 The submission also included results of Quality of Life data instruments recorded in the POLARIS-1 trial.
- 6.14 Overall, there was no meaningful difference in quality of life between placebo and sofosbuvir with velpatasvir and voxilaprevir over the 12 week treatment duration.
- 6.15 Table 6 presents the naïve comparison of sofosbuvir with velpatasvir and voxilaprevir and glecaprevir with pibrentasvir presented in the Appendix to the submission.
- 6.16 The submission stated the data showed glecaprevir with pibrentasvir was effective in achieving an 'acceptable SVR rate' in patients previously treated with an NS5A inhibitor (excluding subjects with genotype 3), but that SVR rates achieved with sofosbuvir with velpatasvir and voxilaprevir in NS5A patients were numerically higher or the same as those achieved with glecaprevir with pibrentasvir in both the overall DAA-failed population and the specific NS5A failed population. This applied to the limited subgroups of prior DAA exposure and prevalence of baseline resistance associated variants (RAVs).

**Table 6: Side-by-side comparison of efficacy results in MAGELLAN-1 and POLARIS-1.**

Outcome	MAGELLAN 1 - GP		POLARIS 1-sof+vel+ox
	12 weeks	16 weeks	12 weeks
	(n=44)	(n=47)	(n=263)
SVR12	39/44 (89%)	43/47 (91%)	253/263 (96.2%)
SVR12 rates in NS5A-experienced patients			
Ns5A only (PI naïve)	14/16 (88%)	17/18 (94%)	151/161 (93.8%)
PI plus NS5A	11/14 (79%)	13/16 (81%)	83/83 (100.0%)
PI only (NS5A naïve)	14/14 (100%)	13/13 (100%)	All patients NS5A experienced
SVR12 rates based on presence of baseline RAV's.			
No RAVs	13/13 (100%)	13/13 (100%)	42/43 (97.7%)
NS3 Only	2/2 (100%)	4/4 (100%)	9/9 (100%)
NS5A Only	20/24 (83 %)	22/23 (96%)	120/124 (96.8%)

GP = glecaprevir with pibrentasvir; NS5A = non-structural protein 5A; RAV = resistance associated variant; sof+vel+vox = sofosbuvir plus velpatasvir plus voxilaprevir; SVR12 = sustained virological response

Source: Tables 6-8, p7-8 of Appendix 3 to the submission.

6.17 The difference in point estimates for overall SVR12 between the sofosbuvir with velpatasvir and voxilaprevir (96%) and 16 week glecaprevir with pibrentasvir arm (91%) was approximately 5%. Though no non-inferiority threshold was presented in the submission, 5% was used as a non-inferiority threshold in the POLARIS-2 non-inferiority trial. With the exception of patients who had been treated with both NS5A and protease inhibitors (PI), the point estimates of SVR 12 for glecaprevir with pibrentasvir 16 weeks tended to be the same or slightly greater than those of sofosbuvir with velpatasvir and voxilaprevir. It was acknowledged that MAGELLAN-1 (Part 2) only included patients with genotypes 1 and 4. The pre-PBAC response argued that the inclusion of only these 2 genotypes in the MAGELLAN-1 trial meant it would be inappropriate to declare non-inferiority of glecaprevir with pibrentasvir to sofosbuvir with velpatasvir and voxilaprevir, and that the results should not be transferrable to patients outside of the GT1 and GT4 population.

### **Comparative harms**

6.18 There was a statistically significant difference in treatment related adverse events, with sofosbuvir with velpatasvir and voxilaprevir associated with a 14% increase compared with placebo, but, overall, the submission's claim of tolerable safety was supported by the POLARIS-1 trial (see Table 7). The ESC noted that the adverse events reported were for all patients treated with sofosbuvir with velpatasvir and voxilaprevir, not only those with genotype 1 to which the placebo data apply.

**Table 7: Summary of key adverse events in POLARIS-1**

Trial ID	Sof+vel+vox N=263 n (%)	Placebo N=152 n (%)	RD (95% CI)
Adverse event	206 (78.3)	107 (70.4)	0.08 (-0.01, 0.17)
Treatment-related adverse Event	145 (55.1)	63 (41.4)	0.14 (0.04, 0.24)
Grade 3 or above adverse event	5 (1.9)	4 (2.6)	-0.01 (-0.04, 0.02)
Grade 3 or above treatment-related adverse event	1 (0.4)	0	0 (0, 0.01)
Serious adverse event	5 (1.9)	7 (4.6)	-0.03 (-0.06, 0.01)
Treatment-related serious adverse event	0	0	0 (0, 0)
Adverse event leading to premature discontinuation	1 (0.4)	3 (2.0)	-0.02 (-0.04, 0.01)
Adverse event Leading to Interruption of the study drug	0	1 (0.7)	-0.01 (-0.02, 0.01)
All death	0	0	0 (0, 0)

CI = confidence interval; n = number of participants reporting data; N = total participants in group; RD = risk difference; RR = relative risk  
Note: risk differences were calculated during the evaluation.

Source: Table 2.22, p63 of the submission.

6.19 Table 8 presents a summary of key adverse events presented in the naïve comparison of glecaprevir with pibrentasvir and sofosbuvir with velpatasvir and voxilaprevir.

**Table 8: Summary of key adverse events for GP and sofosbuvir + velpatasvir + voxilaprevir**

Patients with events, n (%)	Phase 2, Part 2 (all DAA experienced)		POLARIS-1 (all NS5A experienced)
	GP 12 weeks (N=44)	GP 16 weeks (N=47)	Sof+vel+vox 12 weeks (N=263)
Any AE	33 (75%)	32 (68%)	206 (78.3%)
Serious AE	1 (2%)	2 (4%)	5 (1.9%)
Serious AEs	0	0	0
Suspected drug-related			
AEs leading to discontinuation	0	0	1 (0.4%)
Suspected drug-related			

AE = adverse event; DAA = direct acting antiviral; GP = glecaprevir with pibrentasvir; NS5A = non-structural protein 5A; sof+vel+vox = sofosbuvir plus velpatasvir plus voxilaprevir.

Source: Table 9, p8 of Appendix 3 to the submission.

6.20 The submission also considered that the safety and tolerability of sofosbuvir with velpatasvir and voxilaprevir appeared to be comparable based on the available glecaprevir with pibrentasvir data.

### **Benefits/harms**

6.21 On the basis of POLARIS-1 trial presented by the submission, for every 100 patients treated with sofosbuvir with velpatasvir and voxilaprevir in comparison to placebo and over a treatment duration of 12 weeks:

- Approximately 96 additional patients would achieve sustained virological response at 12 weeks.
- Approximately 14 additional patients would have any treatment emergent adverse event.

6.22 On the basis of the naïve comparison of single arms of the POLARIS-1 trial and MAGELLAN-1 trial (Part 2) presented by the submission, the comparison of

sofosbuvir with velpatasvir and voxilaprevir for 12 weeks and glecaprevir with pibrentasvir for 16 weeks resulted in similar a proportion of patients achieving SVR 12 and similar overall tolerability.

### **Clinical claim**

- 6.23 The submission described sofosbuvir with velpatasvir and voxilaprevir as superior in terms of effectiveness compared with standard medical management and having an acceptable safety profile compared with standard medical management. This claim was reasonable.
- 6.24 However, given the positive PBAC recommendation for glecaprevir with pibrentasvir in patients with chronic hepatitis C (CHC) that have failed prior treatment with the use of an NS5A inhibitor (Glecaprevir with pibrentasvir, PBAC web outcome; November 2017), upon PBS-listing, glecaprevir with pibrentasvir would be the appropriate comparator and an explicit clinical claim in comparison to glecaprevir with pibrentasvir was warranted. Acknowledging the submission's concerns regarding the publically available evidence for glecaprevir with pibrentasvir, the ESC considered that based on the evidence provided there was a trend towards greater efficacy with sofosbuvir with velpatasvir and voxilaprevir and that a strong claim of non-inferior efficacy and comparable safety to glecaprevir with pibrentasvir was supported by the comparison.

### **Economic analysis**

- 6.25 The submission presented a cost-utility model based on the claim of superior efficacy and tolerable safety in comparison to standard management (no active treatment). Given that ESC considered glecaprevir with pibrentasvir is likely to be a more appropriate comparator than standard management should it be PBS-listed according to the recommendations of the PBAC, a cost-utility model against standard management may no longer be relevant. Should a claim of non-inferiority to glecaprevir with pibrentasvir be accepted, a cost-minimisation analysis would be appropriate. The ESC considered that on the basis of the evidence provided, sofosbuvir with velpatasvir and voxilaprevir is non-inferior to glecaprevir with pibrentasvir and that a cost-minimisation approach is appropriate. The pre-PBAC response strongly disagreed that glecaprevir with pibrentasvir can be considered the most relevant comparator in all NS5A failures and argued that a cost-minimisation approach is only valid where the patient population is the same in both treatments. The pre-PBAC response further stated that as glecaprevir with pibrentasvir is only TGA-approved in GT1 patients who have failed treatment with an NS5A-containing regimen, that a cost-utility analysis vs 'no active treatment' is the most appropriate economic evaluation patients with genotypes 2-6.

6.26 The basis of that cost-minimisation analysis may be that the equi-effective doses are:  
 one sofosbuvir with velpatasvir and voxilaprevir (400/100/100mg) tablet once daily for 12 weeks is equivalent to glecaprevir with pibrentasvir (100mg/40mg) three tablets daily (total daily dose of 300mg/120mg) for 16 weeks.

6.27 Consideration of any differences in monitoring costs may also be relevant within the cost-minimisation analysis. The submission’s cost-utility analysis included specific monitoring costs based on the sofosbuvir with velpatasvir and voxilaprevir PI, the Australian HCV Consensus statement and the Kirby report, totalling \$324. Ultimately, any cost-minimisation approach should ensure that the cost of a 12week course of sofosbuvir with velpatasvir and voxilaprevir would be no greater than the effective price of a 16-week course of glecaprevir with pibrentasvir. In the PSCR and pre-PBAC response , the sponsor argues that monitoring costs would not be relevant in a cost-minimisation analysis, noting the monitoring costs presented in the submission were from the cost-utility analysis and are in addition to standard medical management.

**Drug cost/patient/course: \$ [REDACTED] (effective price)**

6.28 The cost of sofosbuvir with velpatasvir and voxilaprevir per course per patient is \$ [REDACTED], based on a weighted DPMQ of \$ [REDACTED] per 4 weeks for a 12-week course.

**Estimated PBS usage & financial implications**

6.29 This submission was not considered by DUSC. The submission took a market share approach to estimate financial impact.

6.30 Table 9 presents the estimated use and financial implications associated with listing sofosbuvir with velpatasvir and voxilaprevir.

**Table 9: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients treated	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<b>Estimated financial implications of sof+vel+vox</b>						
Cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Copayments	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Cost to PBS/RPBS less copayments	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
<b>Net financial implications</b>						
Net cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to MBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to PBS/RPBS/MBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme. Costs to PBS/RPBS and co-payments were back-calculated during the evaluation. Source: Table 4.7 p123, Table 4.9, p124, and Table 4.10, p126 of the submission.

The redacted table shows that at year 6, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be less than \$10 million per year.

- 6.31 The financial estimates were unlikely to be accurate for multiple reasons. First, the submission's forecasting of the total NS5A market was not adequately justified and appeared to be extremely low, leading to significantly underestimated use. In the PSCR the sponsor stated that they were confident in the uptake estimates provided and are willing to work with the Department to ensure the potential cost of listing sofosbuvir with velpatasvir and voxilaprevir is appropriately quantified. Second, there was substantial uncertainty around the real-world evidence for SVR in patients treated with NS5A containing regimens due to missing data in the REACH C observational study SVR results. This had a high impact on financial estimates, and the submission's base case included the lowest possible value. Lastly, the submission's estimates assumed that no therapies would be replaced in the listing of sofosbuvir with velpatasvir and voxilaprevir. This was unrealistic as other DAAs are currently being used in some NS5A experienced patients and glecaprevir with pibrentasvir was recently recommended by the PBAC for NS5A experienced patients. The PSCR noted that if recommended for listing, sofosbuvir with velpatasvir and voxilaprevir would likely join the existing Risk Sharing Arrangement (RSA) for other drugs for the treatment of HCV – as per the November 2017 recommendation for glecaprevir with pibrentasvir. As such, the sponsor argued that the issues identified with the financial estimates may result in only small changes to the forecast impact to PBS budgets.
- 6.32 There is also potential for sofosbuvir with velpatasvir and voxilaprevir to be used beyond the requested restriction, specifically in patients who are NS5A-naïve.

## **7 PBAC Outcome**

- 7.1 The PBAC deferred making a recommendation on the listing of sofosbuvir with velpatasvir and voxilaprevir without discussion, to allow further consideration of the issues raised within the sponsor's pre-PBAC response. The PBAC also considered that further consultation was required on the proposed changes to the HCV treatment matrix given the introduction of new DAA treatments since the general statement was developed.
- 7.2 The PBAC noted that this submission is not eligible for an Independent Review as it was deferred.

### **Outcome:**

Deferred

## **8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to

recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

## **9 Sponsor's Comment**

Gilead Sciences was disappointed to learn that the Committee had deferred making a recommendation without discussion at the PBAC meeting. It is unclear why the efficacy, safety or cost effectiveness of sofosbuvir with velpatasvir and voxilaprevir in the requested patient population was not considered at the March meeting. The proposed use of sofosbuvir with velpatasvir and voxilaprevir is straightforward and clear to proposed prescribers. The PBS listing of sofosbuvir with velpatasvir and voxilaprevir can be readily implemented prior to any revision of the treatment matrix and/or General Statement. Access to an effective, evidence-based treatment for patients who have failed a prior NS5A containing regimen is critical in ensuring the Australian Government meet its commitment to eradicate HCV. Providing a timely, effective and safe treatment for all HCV patients who are NS5A experienced, regardless of genotype and the presence or absence of compensated cirrhosis, is the remaining unmet medical need in HCV. The deferral of sofosbuvir with velpatasvir and voxilaprevir delays access to the last option to cure their HCV for this small but important patient population. Gilead will continue to work to progress a PBS listing of sofosbuvir with velpatasvir and voxilaprevir at the earliest opportunity.

**Addendum to the March 2018 PBAC Minutes:**

**5.11 SOFOSBUVIR with VELPATASVIR and VOXILAPREVIR,  
400mg/100mg/100mg tablets,  
VOSEVI<sup>®</sup>,  
Gilead Sciences Pty Limited.**

**10 Background**

- 10.1 Subsequent to the March 2018 PBAC meeting, the PBAC considered matters relating to the treatment matrix in the General Statement for Drugs for the Treatment of Hepatitis C at its April 2018 Special meeting. The PBAC noted the sofosbuvir with velpatasvir with voxilaprevir (SOF/VEL/VOX) submission had requested an additional treatment category be added to the existing treatment matrix for patients who had previously failed treatment with an NS5A-based treatment regimen. The PBAC considered that while there was some benefit in this approach, it would add additional complexity to the existing treatment matrix. Noting changes in treatment patterns and the introduction of new DAA treatment regimens since the development of the general statement, the PBAC considered that there may be an opportunity to simplify the existing treatment matrix and general statement going forward.
- 10.2 The PBAC recalled it had deferred the SOF/VEL/VOX submission without discussion to further consider matters relating to the General Statement and treatment matrix. As further consideration of the General Statement occurred at its April 2018 Special Meeting, the PBAC considered it may be appropriate to consider recommending SOF/VEL/VOX for PBS listing out of session, under the same conditions as glecaprevir with pibrentasvir (GLE/PIB), which was recommended by the PBAC at its November 2017 meeting.

- 10.3 SOF/VEL/VOX was listed on the ARTG on 25 May 2018 with the following indications:
- VOSEVI (sofosbuvir/velpatasvir/voxilaprevir fixed-dose combination) is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adult patients, without cirrhosis or with compensated cirrhosis, who have:
    - genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor;
    - genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.

## 11 PBAC Outcome

- 11.1 The PBAC recommended, out of session, the listing of sofosbuvir with velpatasvir with voxilaprevir (SOF/VEL/VOX) for the treatment patients with chronic hepatitis C virus (HCV) infection, regardless of genotype, who have failed treatment with an NS5A-based treatment regimen on a cost minimisation basis with glecaprevir with pibrentasvir (GLE/PIB), under the same listing conditions as GLE/PIB.
- 11.2 The PBAC considered that no treatment was not the appropriate comparator for genotypes 2 - 6, and considered that in the context of the recent recommendation for GLE/PIB, (which included those patients with prior NS5A treatment) for HCV genotypes 1-6, with or without cirrhosis<sup>1</sup>, that GLE/PIB was a more appropriate comparator for all treatment-experienced patients in the Australian context.
- 11.3 The PBAC acknowledged there was a place for SOF/VEL/VOX in the treatment of treatment-experienced genotype 3 patients (for whom other treatments have not proven to be effective), but considered there was a significant risk of leakage to treatment-naïve patients and to treatment-experienced patients of other genotypes, for whom effective alternative treatments exist.
- 11.4 The PBAC noted the outcomes of the MAGELLAN-1 (GLE/PIB) and POLARIS-1 (SOF/VEL/VOX) trials presented in the submission (Table 6 refers) which demonstrated similar sustained virologic response rates (SVR12) between the two treatments, particularly in NS5A-experienced patients. The PBAC considered that a claim of non-inferior comparative effectiveness between the two treatments was supported by the clinical evidence.
- 11.5 The PBAC noted the safety comparison of the GLE/PIB and SOF/VEL/VOX trials in the NS5A-experienced population (Table 8 refers), and considered that a claim of non-inferior comparative safety was supported by the clinical evidence.

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<sup>1</sup> Glecaprevir with pibrentasvir public summary document, PBAC November 2017 meeting, paragraph 7.1

- 11.6 The PBAC considered that listing SOF/VEL/VOX on a cost minimisation basis with the other pan-genotypic treatments, under the same risk sharing arrangements as existing drugs used for the treatment of hepatitis C, was appropriate and consistent with its previous recommendations.
- 11.7 With regards to the General Statement for Drugs for the Treatment of Hepatitis C and the proposed additions in the submission, the PBAC reiterated its desire to simplify the existing treatment matrix in order to facilitate greater uptake of treatment in primary care, and felt that further complicating the existing treatment matrix as requested could negatively impact the overall objectives of Hepatitis C elimination initiatives. On this basis, the PBAC considered that SOF/VEL/VOX should be listed under the same listing conditions as GLE/PIB, without additional elements being added to the existing HCV treatment matrix. The PBAC noted, however, that it had recommended further consultation on the authority requirements and HCV treatment matrix going forward.
- 11.8 The PBAC recommended that SOF/VEL/VOX should have the same nurse practitioner prescribing arrangements as other HCV treatments listed under the General Statement. Currently HCV treatments under the General Statement are listed for prescribing by authorised nurse practitioners under the General Schedule only. Medicines for the treatment of hepatitis C are not listed for prescribing by authorised nurse practitioners under the S100 Highly Specialised Drugs Program.
- 11.9 The PBAC recommended that the Early Supply Rule should apply.

## **12 Recommended listing**

Add new item:

Public Summary Document – March 2018 PBAC Meeting

Name, Restriction, Manner of administration and form	Max qty packs	Max qty units	No. of Rpts	Proprietary Name and Manufacturer
SOFOSBUVIR + VELPATASVIR & VOXILAPREVIR Tablet 400mg/100mg/100mg, 28	1	1	2	Vosevi® Gilead Sciences Pty Limited
<b>Category/ Program</b>	GENERAL – General Schedule (Code GE)			
<b>Prescriber type</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives			
<b>Severity:</b>	Chronic			
<b>Condition:</b>	Hepatitis C infection			
<b>PBS Indication:</b>	Chronic Hepatitis C infection			
<b>Restriction:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined			
<b>Clinical criteria:</b>	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.			
<b>Administrative Advice</b>	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.			

Public Summary Document – March 2018 PBAC Meeting

Name, Restriction, Manner of administration and form	Max qty packs	Max qty units	№.of Rpts	Proprietary Name and Manufacturer
SOFOSBUVIR + VELPATASVIR & VOXILAPREVIR				Vosevi® Gilead Sciences Pty Limited
Tablet 400mg/100mg/100mg, 28	1	1	2	
<b>Category/ Program</b>	Section 100 – Highly Specialised Drugs Program – Private Hospitals (Code HS)			
<b>Prescriber type</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives			
<b>Severity:</b>	Chronic			
<b>Condition:</b>	Hepatitis C infection			
<b>PBS Indication:</b>	Chronic Hepatitis C infection			
<b>Restriction:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined			
<b>Clinical criteria:</b>	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.			
<b>Administrative Advice</b>	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.			

Name, Restriction, Manner of administration and form	Max qty packs	Max qty units	№.of Rpts	Proprietary Name and Manufacturer
SOFOSBUVIR + VELPATASVIR & VOXILAPREVIR Tablet 400mg/100mg/100mg, 28	1	1	2	Vosevi® Gilead Sciences Pty Limited
<b>Category/ Program</b>	Section 100 – Highly Specialised Drugs Program – Public Hospitals (Code HB)			
<b>Prescriber type</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives			
<b>Severity:</b>	Chronic			
<b>Condition:</b>	Hepatitis C infection			
<b>PBS Indication:</b>	Chronic Hepatitis C infection			
<b>Restriction:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined			
<b>Clinical criteria:</b>	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.			
<b>Administrative Advice</b>	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.			

## General Statement for Drugs for the Treatment of Hepatitis C

Use the following criteria to determine patient eligibility for subsidisation under the PBS for hepatitis C treating agents.

By writing a PBS prescription, the prescriber is certifying the patient satisfies the qualifying criteria set out below and the use in accordance with the registered indications which differ between agents in this class – refer to the current Product Information for details.

<p><b>Population criteria:</b></p> <p>Patient must be aged 18 years or older.</p>
<p><b>Treatment criteria:</b></p> <p>Must be treated by a medical practitioner or an authorised nurse practitioner<sup>[1]</sup> 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.</p>
<p>The following information must be provided at the time of application:</p> <p>a) the hepatitis C virus genotype; and b) the patient's cirrhotic status (non-cirrhotic or cirrhotic)</p> <p>The following information must be documented in the patient's medical records:</p> <p>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); and b) evidence of the hepatitis C virus genotype</p>

The following matrices identify the regimens which are available for PBS prescription for eligible patients, based on the hepatitis C virus genotype and treatment history.

### Hepatitis C - Non-cirrhotic patients

	Treatment naïve	Treatment experienced
<b>Genotype 1</b>	<b>LEDIPASVIR + SOFOSBUVIR</b> [8 or 12 weeks] <sup>[2]</sup>	<b>LEDIPASVIR + SOFOSBUVIR</b> [12 weeks]
	OR	OR
	<b>DACLATASVIR and SOFOSBUVIR</b> [12 weeks]	<b>DACLATASVIR and SOFOSBUVIR</b> [12 or 24 weeks]
	OR	OR
	<b>SOFOSBUVIR and PEG-IFN and RBV</b> [12 weeks]	<b>SOFOSBUVIR and PEG-IFN and RBV</b> [12 weeks]
OR	OR	
	<b>PARITAPREVIR + RITONAVIR + OMBITASVIR (&amp; DASABUVIR)</b>	<b>PARITAPREVIR + RITONAVIR + OMBITASVIR (&amp; DASABUVIR)</b>

	Treatment naïve	Treatment experienced
	<p>[12 weeks] [3]</p> <p>OR</p> <p><b>PARITAPREVIR + RITONAVIR + OMBITASVIR (&amp; DASABUVIR (&amp; RBV</b></p> <p>[12 weeks] [4]</p> <p>OR</p> <p><b>GRAZOPREVIR + ELBASVIR</b></p> <p>[12 weeks]</p> <p>OR</p> <p><b>SOFOSBUVIR + VELPATASVIR</b></p> <p>[12 weeks]</p> <p>OR</p> <p><b>GLECAPREVIR + PIBRENTASVIR</b></p> <p>[8 weeks]</p>	<p>[12 weeks] [3]</p> <p>OR</p> <p><b>PARITAPREVIR + RITONAVIR + OMBITASVIR (&amp; DASABUVIR (&amp; RBV</b></p> <p>[12 weeks] [4]</p> <p>OR</p> <p><b>GRAZOPREVIR + ELBASVIR</b></p> <p>[12 weeks]</p> <p>OR</p> <p><b>GRAZOPREVIR + ELBASVIR and RBV</b></p> <p>[16 weeks] [5]</p> <p>OR</p> <p><b>SOFOSBUVIR + VELPATASVIR</b></p> <p>[12 weeks]</p> <p>OR</p> <p><b>GLECAPREVIR + PIBRENTASVIR</b></p> <p>[8 or 16 weeks][6]</p> <p><b>SOFOSBUVIR + VELPATASVIR + VOXILAPREVIR</b></p> <p>[12 weeks][11]</p>
<b>Genotype 2</b>	<p><b>SOFOSBUVIR and RBV</b></p> <p>[12 weeks]</p> <p>OR</p> <p><b>SOFOSBUVIR + VELPATASVIR</b></p>	<p><b>SOFOSBUVIR and RBV</b></p> <p>[12 weeks]</p> <p>OR</p> <p><b>SOFOSBUVIR + VELPATASVIR</b></p>

	Treatment naïve	Treatment experienced
	<p>[12 weeks]</p> <p>OR</p> <p><b>GLECAPREVIR + PIBRENTASVIR</b> [8 weeks]</p>	<p>[12 weeks]</p> <p>OR</p> <p><b>GLECAPREVIR + PIBRENTASVIR</b> [8 or 16 weeks][6]</p> <p><b>SOFOSBUVIR + VELPATASVIR + VOXILAPREVIR</b> [12 weeks][11]</p>
<b>Genotype 3</b>	<p><b>DACLATASVIR and SOFOSBUVIR</b> [12 weeks]</p> <p>OR</p> <p><b>SOFOSBUVIR and RBV</b> [24 weeks]</p> <p>OR</p> <p><b>SOFOSBUVIR and PEG-IFN and RBV</b> [12 weeks]</p> <p>OR</p> <p><b>SOFOSBUVIR + VELPATASVIR</b> [12 weeks]</p> <p>OR</p> <p><b>GLECAPREVIR + PIBRENTASVIR</b> [8 weeks]</p>	<p><b>DACLATASVIR and SOFOSBUVIR</b> [12 weeks]</p> <p>OR</p> <p><b>SOFOSBUVIR and RBV</b> [24 weeks]</p> <p>OR</p> <p><b>SOFOSBUVIR and PEG-IFN and RBV</b> [12 weeks]</p> <p>OR</p> <p><b>SOFOSBUVIR + VELPATASVIR</b> [12 weeks]</p> <p>OR</p> <p><b>GLECAPREVIR + PIBRENTASVIR</b> [8 or 16 weeks][6]</p> <p><b>SOFOSBUVIR + VELPATASVIR + VOXILAPREVIR</b> [12 weeks][11]</p>
<b>Genotype</b>	<b>SOFOSBUVIR and PEG-IFN and RBV</b>	<b>SOFOSBUVIR and PEG-IFN and RBV</b>

	Treatment naïve	Treatment experienced
<b>4</b>	<p>[12 weeks]</p> <p>OR</p> <p><b>GRAZOPREVIR + ELBASVIR</b> [12 weeks]</p> <p>OR</p> <p><b>SOFOSBUVIR + VELPATASVIR</b> [12 weeks]</p> <p>OR</p> <p><b>GLECAPREVIR + PIBRENTASVIR</b> [8 weeks]</p>	<p>[12 weeks]</p> <p>OR</p> <p><b>GRAZOPREVIR + ELBASVIR</b> [12 weeks]</p> <p>OR</p> <p><b>GRAZOPREVIR + ELBASVIR and RBV</b> [16 weeks] [5]</p> <p>OR</p> <p><b>SOFOSBUVIR + VELPATASVIR</b> [12 weeks]</p> <p>OR</p> <p><b>GLECAPREVIR + PIBRENTASVIR</b> [8 or 16 weeks][6]</p> <p><b>SOFOSBUVIR + VELPATASVIR + VOXILAPREVIR</b> [12 weeks][11]</p>
<b>Genotype 5 &amp; 6</b>	<p><b>SOFOSBUVIR and PEG-IFN and RBV</b> [12 weeks]</p> <p>OR</p> <p><b>SOFOSBUVIR + VELPATASVIR</b> [12 weeks]</p> <p>OR</p> <p><b>GLECAPREVIR + PIBRENTASVIR</b> [8 weeks]</p>	<p><b>SOFOSBUVIR and PEG-IFN and RBV</b> [12 weeks]</p> <p>OR</p> <p><b>SOFOSBUVIR + VELPATASVIR</b> [12 weeks]</p> <p>OR</p> <p><b>GLECAPREVIR + PIBRENTASVIR</b> [8 or 16 weeks][6]</p> <p><b>SOFOSBUVIR + VELPATASVIR + VOXILAPREVIR</b></p>

	Treatment naïve	Treatment experienced
		[12 weeks][11]

KEY

- PEG-IFN- peginterferon alfa-2a
- RBV – ribavirin

**Hepatitis C – Cirrhotic patients**

	Treatment naïve	Treatment experienced
Genotype 1	<b>LEDIPASVIR + SOFOSBUVIR</b> [12 weeks]	<b>LEDIPASVIR + SOFOSBUVIR</b> [24 weeks]
	OR	OR
	<b>DACLATASVIR and SOFOSBUVIR and RBV</b> [12 weeks]	<b>DACLATASVIR and SOFOSBUVIR</b> [24 weeks]
	OR	OR
	<b>DACLATASVIR and SOFOSBUVIR</b> [24 weeks]	<b>DACLATASVIR and SOFOSBUVIR and RBV</b> [12 weeks]
	OR	OR
	<b>SOFOSBUVIR and PEG-IFN and RBV</b> [12 weeks]	<b>SOFOSBUVIR and PEG-IFN and RBV</b> [12 weeks]
	OR	OR
	<b>PARITAPREVIR + RITONAVIR + OMBITASVIR (&amp;) DASABUVIR (&amp;) RBV</b> [12 weeks]	<b>PARITAPREVIR + RITONAVIR + OMBITASVIR (&amp;) DASABUVIR (&amp;) RBV</b> [12 or 24 weeks] [8]

	Treatment naïve	Treatment experienced
	<p>OR</p> <p><b>GRAZOPREVIR</b> + <b>ELBASVIR</b> [12 weeks]</p> <p>OR</p> <p><b>SOFOBUVIR</b> + <b>VELPATASVIR</b> [12 weeks][7]</p> <p>OR</p> <p><b>GLECAPREVIR + PIBRENTASVIR</b> [12 weeks]</p>	<p>OR</p> <p><b>GRAZOPREVIR</b> + <b>ELBASVIR</b> [12 weeks]</p> <p>OR</p> <p><b>GRAZOPREVIR</b> + <b>ELBASVIR</b> and <b>RBV</b> [16 weeks] [5]</p> <p>OR</p> <p><b>SOFOBUVIR</b> + <b>VELPATASVIR</b> [12 weeks][7]</p> <p>OR</p> <p><b>GLECAPREVIR + PIBRENTASVIR</b> [12 or 16 weeks][6]</p> <p><b>SOFOBUVIR + VELPATASVIR + VOXILAPREVIR</b> [12 weeks][11]</p>
Genotype 2	<p><b>SOFOBUVIR</b> and <b>RBV</b> [12 weeks]</p> <p>OR</p> <p><b>SOFOBUVIR</b> + <b>VELPATASVIR</b> [12 weeks][7]</p> <p>OR</p> <p><b>GLECAPREVIR + PIBRENTASVIR</b> [12 weeks]</p>	<p><b>SOFOBUVIR</b> and <b>RBV</b> [12 weeks]</p> <p>OR</p> <p><b>SOFOBUVIR</b> + <b>VELPATASVIR</b> [12 weeks][7]</p> <p>OR</p> <p><b>GLECAPREVIR + PIBRENTASVIR</b> [12 or 16 weeks][6]</p> <p><b>SOFOBUVIR + VELPATASVIR + VOXILAPREVIR</b> [12 weeks][11]</p>

	Treatment naïve	Treatment experienced
Genotype 3	<b>SOFOBUVIR and RBV</b> [24 weeks]	<b>DACLATASVIR and SOFOBUVIR</b> [24 weeks]
	OR	OR
	<b>DACLATASVIR and SOFOBUVIR</b> [24 weeks]	<b>SOFOBUVIR and RBV</b> [24 weeks]
	OR	OR
	<b>SOFOBUVIR and PEG-IFN and RBV</b> [12 weeks]	<b>SOFOBUVIR and PEG-IFN and RBV</b> [12 weeks]
	OR	OR
	<b>DACLATASVIR and SOFOBUVIR and RBV</b> [12 or 24 weeks] [9]	<b>DACLATASVIR and SOFOBUVIR and RBV</b> [12 or 24 weeks] [9]
OR	OR	
<b>SOFOBUVIR + VELPATASVIR</b> [12 weeks][7][10]	<b>SOFOBUVIR + VELPATASVIR</b> [12 weeks][7][10]	
OR	OR	
<b>GLECAPREVIR + PIBRENTASVIR</b> [12 weeks]	<b>GLECAPREVIR + PIBRENTASVIR</b> [12 or 16 weeks][6]	
	<b>SOFOBUVIR + VELPATASVIR + VOXILAPREVIR</b> [12 weeks][11]	
Genotype 4	<b>SOFOBUVIR and PEG-IFN and RBV</b> [12 weeks]	<b>SOFOBUVIR and PEG-IFN and RBV</b> [12 weeks]
	OR	OR
	<b>GRAZOPREVIR + ELBASVIR</b>	<b>GRAZOPREVIR + ELBASVIR</b>

	Treatment naïve	Treatment experienced
	<p>[12 weeks]</p> <p>OR</p> <p><b>SOFOBUVIR + VELPATASVIR</b> [12 weeks][7]</p> <p>OR</p> <p><b>GLECAPREVIR + PIBRENTASVIR</b> [12 weeks]</p>	<p>[12 weeks]</p> <p>OR</p> <p><b>GRAZOPREVIR + ELBASVIR and RBV</b> [16 weeks] [5]</p> <p>OR</p> <p><b>SOFOBUVIR + VELPATASVIR</b> [12 weeks][7]</p> <p>OR</p> <p><b>GLECAPREVIR + PIBRENTASVIR</b> [12 or 16 weeks][6]</p> <p><b>SOFOBUVIR + VELPATASVIR + VOXILAPREVIR</b> [12 weeks][11]</p>
<b>Genotype 5 &amp; 6</b>	<p><b>SOFOBUVIR and PEG-IFN and RBV</b> [12 weeks]</p> <p>OR</p> <p><b>SOFOBUVIR + VELPATASVIR</b> [12 weeks][7]</p> <p>OR</p> <p><b>GLECAPREVIR + PIBRENTASVIR</b> [12 weeks]</p>	<p><b>SOFOBUVIR and PEG-IFN and RBV</b> [12 weeks]</p> <p>OR</p> <p><b>SOFOBUVIR + VELPATASVIR</b> [12 weeks][7]</p> <p>OR</p> <p><b>GLECAPREVIR + PIBRENTASVIR</b> [12 or 16 weeks][6]</p> <p><b>SOFOBUVIR + VELPATASVIR + VOXILAPREVIR</b> [12 weeks][11]</p>

KEY

- PEG-IFN - peginterferon alfa-2a
- RBV – ribavirin

[1] Medicines for the treatment of hepatitis C are listed for prescribing by authorised nurse practitioners under the General Schedule only. Medicines for the treatment of hepatitis C are not listed for prescribing by authorised nurse practitioners under the S100 Highly Specialised Drugs Program.

[2] [LEDIPASVIR + SOFOSBUVIR] for treatment-naïve, non-cirrhotic patients:

- consider treatment for 8 weeks where pre-treatment HCV RNA is less than 6 million IU/mL;
- otherwise treatment for 12 weeks where pre-treatment HCV RNA is 6 million IU/mL or greater.

[3] [PARITAPREVIR + RITONAVIR + OMBITASVIR (&) DASABUVIR] for treatment-naïve and treatment experienced, non-cirrhotic patients, treatment for 12 weeks in patients with genotype 1b HCV.

[4] [PARITAPREVIR + RITONAVIR + OMBITASVIR (&) DASABUVIR (&) RBV] for treatment-naïve and treatment experienced, non-cirrhotic patients, treatment for 12 weeks in patients with genotype 1a HCV.

[5] [GRAZOPREVIR + ELBASVIR and RBV] for treatment-experienced, non-cirrhotic and cirrhotic patients, treatment for 16 weeks in patients with genotype 1a or 4 HCV who have experienced on-treatment virologic failure to prior treatment.

[6] [GLECAPREVIR + PIBRENTASVIR] for treatment experienced patients with genotype 3 HCV and patients who have failed an NS5A inhibitor, treatment is for 16 weeks.

[7] [SOFOSBUVIR + VELPATASVIR] for patients with decompensated cirrhosis:

- Use in combination with ribavirin.

[8] [PARITAPREVIR + RITONAVIR + OMBITASVIR (&) DASABUVIR (&) RBV] for treatment-experienced, cirrhotic patients:

- consider treatment for 12 weeks in patients with genotype 1a HCV (except prior null responders to PEG-IFN and RBV) and genotype 1b HCV; or
- consider treatment for 24 weeks in patients with genotype 1a HCV who have had a previous null response to PEG-IFN and RBV.

[9] Consider a 24 week regimen of [DACLATASVIR and SOFOSBUVIR and RBV] for cirrhotic patients where clinically appropriate.

[10] [SOFOSBUVIR + VELPATASVIR] for patients with genotype 3 infection with compensated cirrhosis:

- Consider addition of ribavirin.

[11] [SOFOSBUVIR + VELPATASVIR + VOXILAPREVIR] only for patients who have failed an NS5A inhibitor.

## 13 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.

## 14 Sponsor's Comment

The sponsor had no comment.