5.17 SOFOSBUVIR, 400mg tablet, Sovaldi®, Gilead Sciences Pty Ltd.

1 Purpose of Application

1.1 Section 100 (Highly Specialised Drugs Program), Authority Required (STREAMLINED) listing for sofosbuvir for the treatment of chronic hepatitis C (CHC) in the following populations:

- Treatment naïve, Genotype 1-6;
- Treatment naïve, Genotype 1-3 in patients unsuitable for treatment with interferon based therapy;
- Treatment experienced, Genotype 2 and 3; and,
- Treatment experienced, Genotype 2 and 3 in patients unsuitable for treatment with interferon based therapy.

1.2 The submission had not requested listing for genotypes 4, 5 or 6 treatment naïve patients who are unsuitable for interferon (IFN) therapy, nor for genotypes 1, 4, 5 or 6 for patients who are treatment experienced.

2 Requested listing

2.1 The requested listing is:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
SOFOSBUVIR				Gilead Sciences
Tablet 400mg, 28 tablets	1	5	Sovaldi	Pty Ltd

Section 100 (Highly Specialised Drugs Program)
Authority required (STREAMLINED)

Chronic genotype 1, 2, 3, 4, 5 or 6 hepatitis C infection
The Treatment criteria are:

- Must be treated in an accredited treatment centre,

AND the Clinical criteria are:

- Patient must have compensated liver disease,
- Patient must **not have received prior treatment** with interferon alfa or peginterferon alfa for hepatitis C,
- For patients with genotype 2 HCV infection, the treatment must be in combination with ribavirin and the treatment must be limited to a maximum duration of 12 weeks;
- For patients with HCV genotype 1, 3, 4, 5 or 6 infection who are eligible for treatment with interferon:
    - The treatment must be in combination with peginterferon alfa and ribavirin,
    - The treatment must be limited to a maximum duration of 12 weeks
- For patients with HCV genotype 1 or 3 infection who are unsuitable for treatment with interferon:
    - The treatment must be in combination with ribavirin;
    - The treatment must be limited to a maximum duration of 24 weeks; and

AND the Population criteria are:

- Patient must be 18 years or older,
- Patient must not be pregnant or breastfeeding. Female partners of male patients must not be pregnant. Patients and their partners must each be using an effective form of contraception if of child-bearing age,
- Evidence of chronic hepatitis C infection (repeatedly anti-HCV positive and HCV RNA

positive) must be documented in the patient's medical records,
- Patients with chronic genotype 1 hepatitis C, who have received prior treatment with an NS3/4A protease inhibitor, are not eligible to receive PBS-subsidised sofosbuvir, except where the patient has developed intolerance to the NS3/4A protease inhibitor of a severity necessitating permanent treatment withdrawal.

Chronic genotype 2 or 3 hepatitis C infection

The Treatment criteria are:
- Must be treated in an accredited treatment centre,

AND the Clinical criteria are:
- Patient must have compensated liver disease,
- The patient **must have received prior therapy** with an interferon-based regimen,
- For patients infected with HCV genotype 2:
    - The treatment must be in combination with ribavirin,
    - The treatment must be limited to a maximum duration of 12 weeks,
- For patients infected with HCV genotype 3 who are eligible for treatment with interferon:
    - The treatment must be in combination with ribavirin and peginterferon,
    - The treatment must be limited to a maximum duration of 12 weeks,
- For patients infected with HCV genotype 3 who are unsuitable for treatment with interferon:
    - The treatment must be in combination with ribavirin;
    - The treatment must be limited to a maximum duration of 24 weeks

AND the Population criteria are:
- Patient must be 18 years or older,
- Patient must not be pregnant or breastfeeding. Female partners of male patients must not be pregnant. Patients and their partners must each be using an effective form of contraception if of child-bearing age.
- Evidence of chronic genotype 2 or 3 hepatitis C infection (repeatedly anti-HCV positive and HCV RNA positive) must be documented in the patient's medical records.

2.2 During the evaluation and considerations of the ESC and DUSC, the following points were noted about the restriction:
- For compliance with current electronic media requirements for listing, the Commentary proposed separate restrictions based on prior treatment, genotype and ability to have IFN treatment, and noted that certain wording of the restriction should align with other restrictions of PBS-listed treatments for HCV.
- The ESC noted in the PSCR that the Sponsor is open to discussion about the optimal sofosbuvir regimen for the management of genotype 3 diseases and consideration of excluding genotype 1 treatment naïve IFN unsuitable patients if necessary.
- Specifying 5 repeats was not appropriate for those patients requiring only 12 weeks therapy.
- The PSCR stated that the sponsor would accept making the restriction explicit to exclude a second course of treatment of SOF for genotype 3 disease.
- The ESC considered that, if the proposed treatment population was based on the progression of liver disease /cirrhosis, a fibrotic score measure may be required in the restriction. In the pre-PBAC response, the Sponsor was strongly opposed, stating that: 'The presented evidence supports high cure rates for all patients, regardless of fibrosis stage. In addition, the practical limitations of the FibroScan fibrosis staging method to reliably distinguish contiguous fibrosis stages in patients with moderately severe disease mean the introduction of this element to the PBS restriction would be problematic. Finally, the FibroScan technology is neither widely available nor publicly funded, and clinicians are broadly opposed to the introduction of this eligibility criterion, as reported at the HCV stakeholder meetings (25.2.2014 and 4.5.2012)'.

- The proposed listing for Genotype 1 and Genotype 3 patients states that patients who are unsuitable for a 12 week regimen including interferon would be eligible for a 24 week interferon-free regimen of sofosbuvir. The submission has not defined 'unsuitable', The ESC noted that the PSCR proposed the eligibility criteria in the protocol of the POSITRON trial be used as a starting point for the definition "unsuitable for interferon". The ESC considered that the criteria presented in the PSCR were comprehensive, but may be difficult to implement in the restriction. The DUSC considered that 'unsuitable for interferon' would be broadly interpreted in practice and that given patient aversion to interferon, there was a high likelihood of use beyond the requested restriction. The commentary noted that a key trial of patients who were unsuitable for IFN (POSITRON) included patients who were unwilling to receive IFN, but who were not necessarily contraindicated or intolerant to IFN. In the pre-PBAC response, the Sponsor stated that it was agreeable to specifically excluding 'unwilling' from the definition of "unsuitable for IFN". The Sponsor proposed that the definition of "unsuitable for IFN" in the restriction should be based on clinical parameters that cannot be broadly interpreted in practice is appropriate.
- Ribavirin is not currently listed as a separate product on the PBS, but co-packaged with peginterferon. The PSCR indicates that single agent ribavirin may be accessible under Special Access Scheme (of the TGA, where prescribers can apply for supply of the product on a case by case basis).
- The current PBS listings of telaprevir and boceprevir do not exclude their use following failure with sofosbuvir.
- The ESC considered that the wording of the PBS listing is dependent on the final registered product information (PI). As sofosbuvir was evaluated via the parallel process with the TGA, an updated PI was not provided during the consideration of the submission by the PBAC.
- The proposed PBS listing is inconsistent with the draft PI provided with submission, including:
    - The draft PI [redacted] where the proposed listing includes interferon-based regimens.
    - The treatment duration recommended in the draft PI for interferon-free treatment of patients with genotype 3 HCV is [redacted], while the PBS listing proposes 12 or 24 weeks, depending on treatment regimens.
    - The draft PI [redacted].

2.3 Listing was sought on a cost effectiveness basis of sofosbuvir compared to the comparator appropriate for the HCV Genotype and the patient receiving prior treatment or not and their suitability for treatment with peginterferon (PEG).

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

3 Background

3.1 The submission was made under TGA/PBAC Parallel Process. Sofosbuvir was entered onto the ARTG on 30 June 2014, before PBAC consideration. As the consideration of sofosbuvir advanced via the parallel process with the TGA, an updated PI was not provided.

3.2 This drug had not previously been considered by the PBAC.

4 Clinical place for the proposed therapy

4.1 HCV infection is a major cause of chronic liver disease. The cycle of viral reproduction within hepatic cells and the response by the host immune system to the infection results in damage to the host's liver. Chronic infection can lead to scarring of the liver and ultimately to cirrhosis. In some cases, patients with liver cirrhosis develop liver failure, liver cancer or life-threatening oesophageal and gastric HCV. Currently, Genotype 1 or Genotype 3 account for 88-92% of infections in Australia.

Distribution of HCV Genotypes in Australian CHC patients

HCV Genotype	Gidding et al 2012 (ACHOS subgroup: treatment naïve who went on to receive therapy, used for Section D) (Table C-7 of the submission, pg 8)	Dore et al 2003 (previous Australian studies, 1996-1998, Table C-9 of the submission, pg 9)
1	49.6%	55%
2	5.6%	8%
3	42.2%	33%
4)	-	3%
Unknown (4,6)	2.4%	-
Other/mixed	-	1%

4.2 Currently, the PBS reimburses direct acting antivirals (DAAs), including boceprevir and telaprevir (two HCV NS3/4A inhibitors, both of which must be used in combination with PR), for the treatment of HCV Genotype 1. In addition, the PBS reimburses peginterferon alfa-2a or alfa-2b in combination with ribavirin for the treatment of Genotypes 1-6 HCV.

4.3 Sofosbuvir, which is used in combination with peginterferon and ribavirin is a first in class nucleotide analogue inhibitor of HCV specific NS5B polymerase with activity against all HCV genotypes. Sofosbuvir in combination with ribavirin also provides a therapeutic option for treatment naïve patients with genotypes 1, 2 or 3 HCV and treatment experienced patients with genotypes 2 or 3 HCV who are unsuitable for interferon based therapy.

4.4 The ESC considered that it is difficult to define how sofosbuvir will be used in clinical practice given the rapidly changing treatment combinations that will soon be available to patients. The ESC noted that interferon-free therapy will likely be the treatment preference of patients and clinicians, given many patients, particularly those with asymptomatic infection and no or little liver fibrosis, defer treatment for fear of side effects associated with current treatments and the expectation of new treatment options with higher efficacy and/or a better side effect profile. The ESC considered that simplified interferon-free therapy could broaden access of treatment to patients with limited access to specialised treatment centres such those in regional, rural and remote areas. The ESC noted the results of modelling which suggest that broadening the availability of therapy, including to active intravenous drug users, could significantly impact on HCV transmission (Martin, Hepatology, 2013, 58:1598).

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

5 Comparator

5.1 The appropriate comparator for sofosbuvir is dependent upon the HCV genotype, prior exposure to treatment and suitability for treatment with interferon. The duration

of treatment with the comparator also depends upon the presence or absence of cirrhosis. The following comparators were nominated in the submission:

HCV Genotype	Proposed Comparator (in submission)	Alternate Comparator considering the total pool of individuals with HCV including those eligible for, but deferring, IFN-based therapy (ESC Advice)
Treatment naïve, suitable for IFN		
1	TVR+PEG+RBV (RGT 24-48 weeks) BOC+PEG+RBV (RGT 28-48 weeks)	No treatment
2, 3	PEG+RBV (RGT 24-48 weeks)	No treatment
4, 5, 6	PEG+RBV (RGT 48 weeks)	No treatment
Treatment naïve, unsuitable for IFN		
1, 2, 3	No treatment	No treatment
Treatment experienced, suitable for IFN		
2, 3	No treatment	No treatment
Treatment experienced, unsuitable for IFN		
2, 3	No treatment	No treatment

5.2 Treatment experienced patients with genotype 2 or 3 HCV who are suitable for IFN therapy are eligible for 48 weeks of PEG+RBV, which could be considered to be the comparator. The ESC agreed with the PSCR, that although PEG + RBV (48 weeks) is available, patients are unlikely to be treated with PEG a second time and 'no treatment' is the appropriate comparator.

5.3 The ESC considered that the comparators presented in the submission are appropriate. In the context of the current population with HCV infection in Australia, the ESC considered that many individuals with HCV were deferring treatment based on the slow progress of disease symptoms and the liver damage of the indolent infection, the access to treatment centres, and the expected development of new treatments with shorter, better tolerated, IFN-sparing regimens. Considering the total pool of individuals infected with HCV who might become willing to accept treatment if IFN-free options become available, a more appropriate comparator for all genotypes may be 'no treatment'.

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 (261), health care professionals (25) and organisations (24) via the Consumer Comments facility on the PBS website. The comments described the benefits of treatment with the new drugs for HCV. The benefits identified included changing an infection with HCV from a chronic disease to one that can be cured; a shorter treatment regimen; reduced side effects; injection-free and allowing broader access to treatment.

6.3 The PBAC noted the correspondence from the Transplantation Society of Australia and New Zealand (TSANZ) and the Australian Liver Association (ALA) proposing early access to sofosbuvir containing HCV treatment for liver transplant recipients and patients with cirrhosis complicated by portal hypertension (item 14.8).

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

Clinical trials

6.4 Four clinical studies including sofosbuvir (NEUTRINO, FISSION, POSITRON, FUSION), one including boceprevir (SPRINT-2) and one including telaprevir (ADVANCE) were included in Section B of the submission.

6.5 The submission introduced additional studies in Section C as the basis for the sustained virologic response (SVR) rates which were used in the economic analysis for sofosbuvir (VALENCE, ELECTRON, PROTON, LONESTAR-2, QUANTUM, SPARE) and the comparators (boceprevir, Poordad et al, 2013, and peginterferon ribavirin 48 weeks, Manns et al, 2001). All trials are listed in the Table below.

Trial ID	N	Design/ duration[a]	Risk of bias[c]	Protocol title/ Publication title	Publication citation
Sofosbuvir					
GS-US-334-0110 NEUTRINO	327	Single arm, MC / 24 weeks	High	A phase 3, multicentre, open-label study to investigate the efficacy and safety of GS-7977 with Peginterferon alfa-2a and ribavirin for 12 weeks in treatment-naive subjects with chronic genotype 1,4,5, or 6 HCV infection. Lawitz E et al, Sofosbuvir for previously untreated chronic hepatitis C infection	N Engl J Med 2013; 368(20): 1878-87.
P7797-1231 FISSION	499	R, OL, MC / 24 weeks	Low	A phase 3, multicentre, randomised, active-controlled study to investigate the safety and efficacy of PSI-7977 and ribavirin for 12 weeks compared to pegylated interferon and ribavirin for 24 weeks in treatment-naive patients with chronic genotype 2 or 3 HCV infection. Lawitz E et al, Sofosbuvir for previously untreated chronic hepatitis C infection	N Engl J Med 2013; 368(20): 1878-87.

GS-US-334-0107 POSITRON	278	R, DB, MC / 24 weeks	Low	A phase 3, multicentre, randomised, double-blind, placebo-controlled study to investigate the efficacy and safety of GS-7977 + ribavirin for 12 weeks in subjects with chronic genotype 2 or 3 HCV infection who are interferon intolerant, interferon ineligible or unwilling to take interferon. Jacobson IM et al, Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options.	N Engl J Med 2013. 368(20): 1867-77
GS-US-334-0108 FUSION	103	Single arm[b], MC / 24 weeks	High	A phase 3, multicentre, randomised, double-blind study to investigate the efficacy and safety of GS-7977 + ribavirin for 12 or 16 weeks in treatment experienced subjects with chronic genotype 2 or 3 HCV infection. Jacobson IM et al, Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options.	N Engl J Med 2013. 368(20): 1867-77
VALENCE SOF12+R12 (Section C of the submission, GT2	323			an ongoing phase 3, randomised, double-blind, placebo-controlled study of sofosbuvir + RBV in treatment-naïve or treatment-experienced patients with chronic genotype 2 or 3 HCV infection. The genotype 3 HCV infected patient group received an extended course of treatment with sofosbuvir + RBV, of 24 weeks duration	VALENCE Interim Synoptic CSR 08 October 2013
PROTON SOF12+PR12 (Section C of the submission, GT3)	25 (10 GT3)			Phase 2 dose ranging study in treatment naïve HCV genotype 1, 2, and 3 infected patients. The trial enrolled 25 patients who were treated with sofosbuvir + Peg-IFN + RBV for 12 weeks, of whom 10 were HCV genotype 3 infected patients.	European Medicines Agency, Annex 1: Summary of Product Characteristics (Sovaldi) 2014
ELECTRON SOF12+PR12 (Section C of the submission, GT3)	11 (7 GT3)			Phase 2 open label study of sofosbuvir in treatment naïve HCV genotype 2 or 3 infected patients. The trial enrolled 11 patients who were treated with sofosbuvir + Peg-IFN + RBV for 12 weeks, of whom 7 were HCV genotype 3 infected patients.	European Medicines Agency, Annex 1: Summary of Product Characteristics (Sovaldi) 2014
LONESTAR-2 SOF12+PR12 (Section C of the submission, GT3)	47			open-label, single-arm, Phase 2 study of a 12-week course of sofosbuvir + RBV + Peg-IFN in patients with genotype 2 or 3 HCV infection who had previously failed treatment with an interferon-based regimen.	A full clinical study report is not yet available for the LONESTAR-2 study, although a summary of results is included in the European summary of product characteristics (SmPC)
QUANTUM SOF24+R24 (Section C of the	157			an adaptive study, originally designed to investigate a range of regimens including the investigational agent GS-0938 with and without sofosbuvir and/or	QUANTUM Abbreviated final CSR 10 July 2013

submission, GT1)				ribavirin. The study enrolled treatment naive patients of all HCV genotypes, of whom approximately 80% were genotype 1 and 10% cirrhotic. The study was re-purposed to evaluate the efficacy of sofosbuvir+ ribavirin, after a safety signal mandated discontinuation of the various GS-0938 regimens.	
SPARE SOF24+R24 (Section C of the submission, GT1)				Single-center, randomized, 2-part, open-label phase 2 study involving 60 treatment-naive patients with hepatitis C virus (HCV) genotype 1 enrolled at the National Institutes of Health. Osinusi, A, et al. "Sofosbuvir and ribavirin for hepatitis C genotype 1 patients with unfavourable treatment characteristics: A randomised clinical trial."	JAMA, 2013: 804-811.
Boceprevir					
P05216AM2 SPRINT-2[d]	368	Single arm of R trial[d], MC / up to 72 weeks	High	A Phase 3, Safety and Efficacy Study of Boceprevir in Previously Untreated Subjects With Chronic Hepatitis C Genotype 1 Poordad F. et al 'Boceprevir for untreated chronic HCV genotype 1 infection:	New England Journal of Medicine,2011, vol. 364, no. 13, pp. 1195-1206
Poordad et al, 2013 (Section C of the submission, GT1)	687			a randomised study in genotype 1 patients treated with boceprevir + Peg-IFN,' which assessed the impact on anaemia of RBV dose reduction or erythropoietin. Poordad, F et al. "Effects of ribavirin dose reduction vs erythropoietin for boceprevir-related anemia in patients with chronic hepatitis C virus genotype 1 infection - a randomized trial."	Gastroenterology, 2013: 1035-1044.
Telaprevir					
VX07-950-108 ADVANCE[d]	365	Single arm of R trial[d], MC / up to 72 weeks	High	A Phase 3 study to evaluate the efficacy and safety of two dosing regimens of telaprevir in combination with peginterferon alfa-2a and ribavirin in Treatment-Naive Subjects With Genotype 1 Chronic Hepatitis C Jacobson et al 'Telaprevir for previously untreated chronic hepatitis C virus infection	New England Journal of Medicine, 2011, vol. 364, no. 25, pp. 2405-2416
Peg-IFN + RBV					
Manns et al 2001 PR48 (Section C of the submission)				an open label parallel group study evaluating the optimal Peg-IFN + RBV regimen for use in patients with HCV genotype 1, 4, 5, 6 infection Manns, MP et al. "Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial."	The Lancet, 2001: 958.

[a]Duration of trial is calculated as duration of treatment + required follow up to measure primary efficacy outcome.
[b]FUSION is a randomised trial of sofosbuvir + RBV for 12 weeks vs 16 weeks. The latter arm is not relevant to the submission and the SVR rates (primary outcome) are therefore naïve.
[c]Overall estimate of risk of bias includes bias associated with the nature of the comparison (ie, a comparison of

single arms from different trials has a high risk of bias).
[d]SPRINT-2 and ADVANCE were both randomised, double blind, three arm trials. Only one arm is used in the submission as NEUTRINO has no common comparator arm and therefore a single arm comparison is made. Risk of bias associated with this type of comparison is high.
DB=double blind; MC=multi-centre; OL=open label; R=randomised, IFN=interferon; SVR12/24=sustained virologic response measured at 12 weeks / 24 weeks following end of treatment; GT, genotype

6.6 The ESC noted that the SVR rates from FISSION and POSITRON, the trials with the lowest risk of bias, were not used to inform the economic model. The ESC, also noting the discussion by the Sponsor in the PSCR, considered that the evidence provided in the submission was the best available as the development program of sofosbuvir has been based predominately on single arm trials. To a significant extent the use of single arm trials was due to the perceived loss of clinical equipoise between sofosbuvir-containing and comparator regimens.

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

Comparative effectiveness

6.7 The primary outcome for the clinical trials is whether a patient achieves a sustained virologic response (SVR) at 12 weeks (absence of detectable RNA of the hepatitis C virus 12 weeks after completion of antiviral therapy: SVR12). The ESC provided the following summary table of the clinical efficacy of sofosbuvir against the comparators presented in Section B and Section C, and noted that:

- For all genotypes, the SVR following SOF-containing regimens is greater than the SVR of the comparator
- For treatment naïve patients with Genotype 1 (approximately 50% of all CHC patients), the SVR following SOF is greater than the SVR of the comparator. The SVR was 89% following treatment with SOF12 + PR12 and 65% following treatment with the IFN-free regimen of SOF24 + R24. If patients who were unwilling but suitable for IFN were to be treated with the IFN-free regimen, they would be predicted to achieve a 65% SVR (which is similar to current treatments available on the PBS, 55-75%) instead of an 89% SVR with the IFN-containing 12 week regimen and at a cost of an additional 12 weeks of SOF.
- For treatment naïve/experienced patients with Genotype 3 (approximately 42% of patients with HCV), the SVR with SOF-containing regimens is greater than the SVR of the comparator. If patients unwilling but suitable for IFN were to be treated with the IFN-free regimen, SOF24 + R24, rather than with the IFN-containing regimen, SOF12 + PR12, they could achieve no greater absolute treatment effect but there would be an additional cost for the longer treatment regimen. The SVR rates of patients treated with SOF12 + PR12 are derived from small numbers of patients (24-51).

Summary of the clinical evidence provided in Section B and Section C, ICERs and population weights used in Section D of the submission, summarised by ESC.

Genotype	Treatment subgroup	Proposed	Comparator	Trial	SOF SVR	Comparator SVR	Extra SVRs /100	ICER for population (submission section D)	Population Weights (section D of submission)
GT1	Naïve (N)	SOF12 + PR12	TVR/BOC + PR24/48	NEUTRINO Vs mixed	89%	55-75%	15 or 26	BOC: $45,000/QALY- $75,000QALY TEL: $45,000/QALY- $75,000QALY	BOC: [redacted]% TEL: [redacted]%
	N, IFN-free	SOF24 + R24	None	QUANTUM & SPARE (Sect C)	65%	0	65	IFN unsuitable: $105,000/QALY - 200,000/QALY	IFN unsuitable: [redacted]%
GT2	Naïve	SOF12 + R12	PR24	FISSION	97%	78%	19	IFN eligible: $105,000/QALY- $200,000/QALY IFN unsuitable: $15,000/QALY-	IFN eligible: [redacted]% IFN unsuitable: [redacted]%
	Experienced (Exp)	SOF12 + R12	None	FUSION	31/36 =86%	0	86	IFN eligible: $15,000/QALY- $45,000/QA	IFN eligible: [redacted]% IFN

Genotype	Treatment subgroup	Proposed	Comparator	Trial	SOF SVR	Comparator SVR	Extra SVRs /100	ICER for population (submission section D)	Population Weights (section D of submission)
								LY IFN unsuitable: $15,000/QALY-$45,000/QALY	unsuitable: [redacted]%
GT3	Naïve	SOF12 + PR12	PR24	PROTON/ ELECTRON/ LONESTAR (Sect C) Vs FISSION(comp)	48/51 =94%	63%	34	IFN eligible: $45,000/QALY-$75,000/QALY	IFN eligible [redacted]%
	Exp	SOF12 + PR12	None	LONESTAR	20/24 =83%	0	83	IFN eligible: $15,000/QALY-$45,000/QALY	IFN eligible: [redacted]%

GT3	N/Exp IFN-free	SOF24 + R24	None	VALENCE	98/105 =93% (N) to 113/145 =78% (Exp)	0	78-93	N;IFN eligible: $105,000/QALY- $200,000/QALY N; IFN unsuitable: $63,433 $45,000/QALY- $75,000/QALY Exp; IFN eligible: $75,000/QALY- $105,000/QALY Exp; IFN unsuitable: 75,000/QALY- $105,000/QALY	N; IFN eligible: [redacted]% N; IFN unsuitable: [redacted]% Exp; IFN eligible: [redacted]% Exp; IFN unsuitable; [redacted]%
GT4-6	Naïve	SOF12 + PR12	PR48	NEUTRINO Vs Manns et al.	34/35 =97%	~50%	~47	IFN eligible: $75,000/QALY- $105,000/QALY	IFN eligible; [redacted]%

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

Comparative harms

6.8 The sofosbuvir treatment regimens were shorter (12 weeks) than those of the active comparators (24-48 weeks) and (except for NEUTRINO and LONESTAR) did not contain peginterferon. The safety profile of sofosbuvir appears to be no worse, and may be superior, to those of the active comparators. Compared with placebo, patients receiving sofosbuvir had a greater number of adverse events, although many of these events may have been associated with the co-administered ribavirin. No adverse events unique to sofosbuvir were identified in the included studies. The data for harms were not presented by HCV genotype or treatment experience as it is unlikely that these characteristics would modify treatment toxicity.

	Sofosbuvir	Comparator		Event rate/100 patients			Risk Difference (unadjusted)[a]	
				Sofosbuvir	Comparator			
	NEUTRINO SOF12+PR12	SPRINT-2 BOC+PR28/48	ADVANCE TVR+PR24/48	SOF	BOC	TVR	SOF vs BOC	SOF vs TVR
Treatment-emergent SAE	4/327	42/368	33/363	1.2	11.4	9.1	-10.2	-7.9
AE leading to study discontinuation	5/327	45/368	36/363	1.5	12.2	9.9	-10.7	-8.4
AE leading to modification / interruption of study drug	109/327	146/368	NR	33.3	39.7	-	-6.3	-

	Sofosbuvir	Comparator	Event rate/100 patients		Risk Difference[b]
			Sofosbuvir	Comparator	
FISSION	**SOF12+R12**	**PR24**			
Treatment-emergent treatment related Grade 3 AE	8/256	39/243	3.1	16.0	-12.9
Treatment-emergent SAE	7/256	3/243	2.7	1.2	1.5
AE leading to modification / interruption of study drug	25/256	65/243	9.8	26.7	-17.0
POSITRON	**SOF12+R12**	**PBO**			
Treatment related Grade 2 or higher AE	59/207	12/71	28.5	16.9	11.6
SAE	11/207	2/71	5.3	2.8	2.5
AE leading to modification or interruption of study drug	29/207	0/71	14.0	0	14.0
FUSION	**SOF12+R12**	**SOF16+R16**			
Treatment related Grade 2 or higher AE	29/103	22/98	28.2	22.4	-
SAE	5/103	3/98	4.9	3.1	-
AE leading to modification or interruption of study drug	9/103	7/98	8.7	7.1	-

[a]Comparison of harms between NEUTRINO and SPRINT-2 or ADVANCE is not adjusted using a common comparator indirect analysis approach. Differences in populations may explain some of the differences in

observed adverse events; [b] bolding indicates harms as measured by the point estimate of the risk difference – only one harm disfavoured sofosbuvir relative to an active treatment.
Source: Compiled during the evaluation, Table B.6.14 and Table B.6.16 in the commentary.

6.9 The PBAC noted that for Genotypes 1 and 3 (noting that other genotypes represent a much smaller proportion of the CHC population), the following comparative benefits and harms were estimated. From the evidence in the submission.

Patient group	comparison	Benefits/harms
Genotype 1, treatment naïve, suitable for IFN	for every 100 patients treated with SOF12+PR12 in comparison to BOC24+PR28/48 and TEL24+PR24/48	• Approximately 15-26 additional patients would be expected to achieve an SVR; • Approximately 8-10 fewer patients would experience a serious adverse event; and • Approximately 6 fewer patients would have an adverse event that leads to modification or interruption of the study drug, compared to BOC24+PR28/48.
	for every 100 patients treated with SOF12+PR12 in comparison to no treatment (based on the NEUTRINO trial):	• Approximately 89 additional patients would be expected to achieve an SVR; and • Approximately 1 additional patient would experience a serious adverse event. • Approximately 33 additional patients would have an adverse event that leads to modification or interruption of the study drug
Genotype 3, treatment naïve, suitable for IFN	for every 100 patients treated with SOF12+PR12 in comparison to PR24:	• Approximately 34 additional patients would be expected to achieve SVR Based on the FISSION trial (SOF12+R12, including patients with Genotype 2 and 3), then: • Approximately 1 to 2 additional patients would experience a serious adverse event; • Approximately 17 fewer patients would have an adverse event that leads to the modification or interruption of the study drug.
	On the basis of evidence presented by the submission, for every 100 patients treated with SOF12+PR12 in comparison to no treatment:	• Approximately 94 additional patients would be expected to achieve SVR Based on the FISSION trial (SOF12+R12, including patients with Genotype 2 and 3), then: • Approximately 3 additional patients would experience a serious adverse event • Approximately 10 additional patients would have an adverse event that leads to the modification or interruption of the study drug. •
Genotype 1, treatment naïve, not suitable for IFN	On the basis of the evidence presented by the submission, for every 100 patients treated with SOF12+R12 in comparison to no treatment:	• Approximately 65 additional patients would be expected to achieve an SVR • Comparative harms of the QUANTUM and SPARE trials were not presented in Section B of the submission.

Genotype 3, treatment naive, not suitable for IFN	On the basis of evidence presented by the submission, for every 100 patients treated with SOF24+R24 in comparison to no treatment:	• Approximately 93 additional patients would be expected to achieve an SVR • Comparative harms of the VALAENCE trial was not presented in Section B of the submission.
Genotype 3, treatment experienced, suitable for IFN	On the basis of evidence presented by the submission, for every 100 patients treated with SOF12+PR12 in comparison to no treatment:	• Approximately 83 additional patients would be expected to achieve an SVR Based on the FUSION trial (SOF12+R12, patients with Genotype 2 and 3), then: • Approximately 5 additional patients would experience a serious adverse event; and • Approximately 9 additional patients would have an adverse event that leads to the modification or interruption of the study drug. • Comparative harms of the LONESTAR trial were not presented in Section B of the submission.
Genotype 3, treatment experienced, not suitable for IFN	On the basis of evidence presented by the submission, for every 100 patients treated with SOF24+R24 in comparison to no treatment:	• Approximately 78 additional patients would be expected to achieve an SVR • Comparative harms of the VALAENCE trial were not presented in Section B of the submission.

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

Clinical claim

6.10 The submission claims that treatment with sofosbuvir is superior in efficacy and safety to current standard of care for treatment naïve patients of any genotype, and treatment experienced patients with genotype 2 or 3 hepatitis C.

6.11 The ESC considered that the claim of efficacy, with sofosbuvir prescribed according to the proposed listing, compared with current standard of care, is:

- SOF12 + R12 is superior to no treatment for Genotypes 2 and 3 (treatment experienced or naïve) and not eligible for IFN
- SOF12 + R12 is superior to PR24 for Genotype 2, treatment naïve patients; and
- SOF12 + PR12 is superior to TVR/BOC + PR24 for Genotype 1, treatment naïve patients suitable for IFN therapy.

Based on supplementary data provided in Section C, there is also some evidence to support:

- SOF24 + R24 is superior to no treatment for Genotype 1, treatment naïve and not eligible for IFN
- SOF12 + PR12 is superior to PR24 for Genotype 3, treatment naïve
- SOF24 + R24 is superior to no treatment for Genotype 3 (treatment experienced or naïve) and not eligible for IFN treatment.

6.12 If no treatment is the accepted comparator for all genotypes, sofosbuvir is superior to no treatment.

6.13 The claim of superior safety is not well supported by the evidence presented. Overall, the safety profile of sofosbuvir-containing regimens appears to be superior to active comparators. However, the safety claims for sofosbuvir presented in Section

B of the submission are often non-comparative, or require unadjusted indirect comparisons with appropriate comparators. Currently, patients who are unsuitable for IFN therapy will receive no treatment and in this population, a conclusion of superior safety for sofosbuvir may be inappropriate.

6.14 Overall, the ESC considered that sofosbuvir has superior safety compared to the active comparators and inferior safety compared to no treatment.

6.15 The PBAC considered that the claim of superior comparative effectiveness was reasonably supported by the data in the submission.

6.16 The PBAC considered that the claim of inferior comparative safety to no treatment and superior comparative safety to peginterferon-containing active treatments was reasonably supported by the data in the submission.

Economic analysis

6.17 The submission presents a modelled economic evaluation based on an unadjusted comparison of results from single arms of different studies. The evaluation is structured as a Markov state-transition model with nine health states, that describes the progression of disease over the lifetime. The model captures both on-treatment and off-treatment phases. The ESC considered that the economic model appears appropriate for each single genotype, regimen, comparator, treatment experience, interferon suitability, cirrhotic status. The submission presents 28 separate estimates of the cost-effectiveness and a weighted ICER calculated from the assumed patient distribution in the 28 separate treatment comparisons.

Summary of model structure and rationale

Component	Summary
Cohort size	10,000
Time horizon	Lifetime (cycles until cohort reaches 100 years of age – Patients enter the model at age 47 and the model continues for 53 years in the base case).
Outcomes	QALY, LYG, cases of compensated cirrhosis avoided, cases of decompensated cirrhosis avoided, hepatocellular carcinoma cases avoided, liver transplants avoided, deaths avoided.
Methods used to generate results	State-transition Markov model with two distinct phases (on and off treatment) and nine mutually exclusive health states describing progression of the disease over a lifetime.
Cycle length	Three monthly cycles for the first two years, followed by yearly cycles.
Transition probabilities	Based on literature review.
Discount rate	5% for costs and outcomes
Software package	Excel 2007

Key drivers of the model

Description	Method/Value	Impact, direction
Morbidity and mortality of patients who achieve SVR	Model assumes no increased morbidity and mortality for cirrhotic and non-cirrhotic patients who achieve SVR	Moderate, favours sofosbuvir
Incorrect treatment regimen	Comparator used in the model, or treatment regimen in the comparator arm differed from the recommendations in the PI documents.	Moderate, favours sofosbuvir
Comparative SVR Rates	Based on an unadjusted single arm comparison.	High, unclear
Proportion of patients entering the model with cirrhotic disease	Economic model has assumed that [redacted]% of patients, across all genotypes and treatment experience will enter the model with compensated cirrhosis.	High, unclear.

6.18 While the health states in the model appear reasonable, some concerns remain about the assumptions made about the morbidity and mortality of patients who achieve SVR. Once participants achieve SVR, irrespective of the presence of cirrhosis, they are assumed to face no greater risk of mortality than the general population and have no risk of developing further liver disease. The ESC considered that this is inappropriate and biases the results of the economic evaluation in favour of sofosbuvir. The ESC noted that the extent of bias could not be estimated as a sensitivity analysis could not be performed without modification of the model structure, which would also require appropriate transition probabilities to be sourced. This issue was not addressed by the sponsor in the pre-PBAC response.

6.19 The model assumes that [redacted]% of patients enter the model with cirrhotic disease. The ESC noted this assumption was not justified in the submission and considered that this assumption would be highly likely to underestimate the ICER of the sub-populations. The ESC noted that in the study by Gidding et al (2012) which was the basis of the distribution of genotypes in the submission, 6.4% of treatment naïve patients had cirrhosis. The ESC noted in the clinical trials presented in Section B that the baseline range of participants with cirrhosis was 4.3%-35.3%. For the subset of trials with treatment naïve patients only (FISSION, NEUTRINO, SPRINT-2, ADVANCE), the range was 4.3%-19.6%. The sponsor argued in the pre-PBAC response that applying a range of 4.3%-19.6% of cirrhotic patients in the model would be inappropriate. The sponsor proposed that the most appropriate and informative source of data is from the ACHOS study (1240 Australian CHC patients) and that, amongst this cohort, [redacted]% of the population were cirrhotic.

6.20 The estimates of comparative effectiveness used in the economic model have been based on single-arm comparisons of SVR rates from separate trials and small sample sizes and as such the results of the model remain highly uncertain.

6.21 The submission has presented separate results of the model for each of the eleven population subgroups presented in the table below. The ICERs presented in the submission vary substantially, from 15,000/QALY-$45,000/QALY for genotype 2, treatment naïve and interferon unsuitable patients to $105,000-200,000/QALY in genotype 1, treatment naïve, and interferon unsuitable patients. The ICERS presented in the submission remain largely uncertain due to concerns about the applicability and appropriateness of the treatment effect applied in the model as well as the structural uncertainties outlined above.

6.22 The ESC noted that the PBAC considered that 30 years was a reasonable extrapolation for models of HCV infection in the assessment of the submissions for boceprevir and telaprevir. The ESC noted that, if a 30 year time horizon is applied to the model provided with the submission, the range of ICER is $15,000/QALY - $45,000/QALY for genotype 2, treatment naïve interferon unsuitable to $105,000 - 200,000/QALY for genotype 1, treatment naïve interferon unsuitable.

6.23 The weighted ICER presented in the submission is $45,000-75,000/QALY and is based on weighting the individual cost-effectiveness ratios for each of the eleven proposed population subgroups according to:

- the genotype distribution in Australia, (see point 4.1, ACHOS subgroup: treatment naïve who went on to receive therapy, Gidding et al 2012),
- treatment status ([redacted]% naïve, [redacted]% experience)
- interferon-eligible/unsuitable ([redacted]%/[redacted]% based on expert opinion)
- for genotype 1 interferon eligible patients, it was assumed that [redacted]% currently receive a boceprevir based regimen and [redacted]% a telaprevir based regimen, in line with current PBS prescribing.

The ESC considered that weighted pooling of ICERs to generate a single value is inherently uncertain because of the assumptions, presented above used to calculate the weighting. A weighted ICER cannot reflect the high variability of cost-effectiveness in the sub-populations. The ESC further noted that if relatively more patients are in the earlier stage of disease (non-cirrhotic) or receive long-course IFN-free rather than short-course IFN-containing regimens than assumed in the submission, the estimated weighted ICER is likely to be lower than the actual overall ICER.

Economic Evaluation of sub-groups based on 53 years (as submission) or 30 year time horizon

Population	Sofosbuvir Regimen	Comparator	53 year time horizon	30 year time horizon
Treatment Naïve				
Interferon eligible				
Genotype 1	SOF + RBV + Peg-IFN, 12 weeks	Peg-IFN + RBV + BOC (24-48 weeks)	$45,000-$75,000	$45,000-$75,000
		Peg-IFN + RBV + TEL (24-48 weeks)	$45,000-$75,000	$75,000-$105,000
Genotype 2	SOF + RBV, 12 weeks	Peg-IFN + RBV (24 weeks)	$105,000-$200,000	$105,000-$200,000
Genotype 3	SOF + RBV + Peg-IFN, 12 weeks	Peg-IFN + RBV (24 weeks)	$45,000-$75,000	$75,000-$105,000
	SOF + RBV, 24 Weeks		$105,000-$200,000	$105,000-$200,000
Genotype 4, 5, 6	SOF + RBV + Peg-IFN, 12 weeks	Peg-IFN + RBV (24-48 weeks)	$75,000-$105,000	$75,000-$105,000
Interferon unsuitable				
Genotype 1	SOF + RBV, 24weeks	No treatment	$105,000-$200,000	$105,000-$200,000
Genotype 2	SOF + RBV, 12 weeks	No treatment	$15,000-$45,000	$15,000-$45,000
Genotype 3	SOF + RBV, 24 weeks	No treatment	$45,000-$75,000	$75,000-$105,000
Treatment Experienced				
Interferon eligible				
Genotype 2	SOF + RBV, 12 weeks	No treatment	$15,000-$45,000	$15,000-$45,000
Genotype 3	SOF + RBV + Peg-IFN, 12 weeks	No treatment	$31,450	$38,719
	SOF + RBV, 24 Weeks		$75,000-$105,000	$75,000-$105,000
Interferon unsuitable				
Genotype 2	SOF + RBV, 12 weeks	No treatment	$15,000-$45,000	$15,000-$45,000
Genotype 3	SOF + RBV 24 weeks	No treatment	$75,000-$105,000	$75,000-$105,000

Abbreviations: SOF = sofosbuvir; BOC = boceprevir; TPV = telaprevir; Peg-IFN = peginterferon + ribavirin; RBV = ribavirin; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year

6.24 The submission presented a variety of univariate sensitivity analyses for the three largest population subgroups:

- Genotype 1, treatment naïve, interferon eligible, compared with boceprevir RBV + Peg-IFN;
- Genotype 3, treatment naïve, interferon eligible, compared with RBV + Peg-IFN ; and,

- Genotype 3, treatment experienced interferon eligible compared with no treatment.

6.25 The model is most sensitive to:

- SVR rates for the respective treatment regimens (ie SOF SVR12 or comparator SVR24);
- Background transition probabilities, in particular those for,
  - non-cirrhotic to compensated cirrhosis; and
  - compensated to decompensated cirrhosis;
- The acquisition costs for sofosbuvir (and boceprevir in GT1);
- The proportion of patients who are cirrhotic at baseline; and
- The discount rate applied to the analysis.

6.26 The ESC noted that the relative effect of each of the translation issues explored in sensitivity analysis in the submission was different for each genotype. For example, excluding discounting, for Genotype 1, treatment naïve, interferon-eligible, compared with boceprevir, the model was most sensitive to costs of sofosbuvir for non-cirrhotic disease. For Genotype 3, treatment experienced interferon-eligible, the model was most sensitive to the transition probabilities for compensated cirrhosis to decompensated cirrhosis .

6.27 The pre-PBAC response provided additional analysis of the cost-effectiveness of treatment of the larger patient populations, namely those infected with GT1 and GT3, assuming no treatment as the comparator, a 30 year time horizon, treatment naïve and IFN eligible or unsuitable. The base case assumed % of patients had cirrhosis and additional sensitivity analysis was presented around this assumption as suggested by the ESC % to %:

	Treatment Naïve interferon unsuitable (SOF + RBV 24 weeks).		Treatment Naïve interferon eligible (SOF + PR 12 Weeks)	
	Genotype 1 (ICER/QALY)	Genotype 3 (ICER/QALY)	Genotype 1 (ICER/QALY)	Genotype 3 (ICER/QALY)
100% cirrhosis	$105,000-200,000	$15,000-45,000	$15,000-45,000	$15,000-45,000
30% cirrhosis (base case)	$105,000-200,000	$75,000-105,000	$15,000-45,000	$15,000-45,000
19.6% (ESC upper limit)	$105,000-200,000	$75,000-105,000	$45,000-75,000	$45,000-75,000
4.3% (ESC lower limit)	$105,000-200,000	$75,000-105,000	$45,000-75,000	$15,000-45,000
No cirrhosis	$105,000-200,000	$105,000-200,000	$45,000-75,000	$45,000-75,000

6.28 The drug cost/patient/12 week treatment is $ (excluding cost of peginterferon + ribavirin). For 24 weeks, the drug cost/patient/ is $ (excluding cost of ribavirin).

6.29 Ribavirin is not PBS listed. An assumed price of ribavirin was inconsistently applied in the models of Section D ($, ribavirin 200mg / 140 tablets) and Section E ($, ribavirin 400mg or 600mg/ 28 tablets). If using the treatment course assumption in Section E of 1000mg ribavirin/day (1 tablet each of 400mg and 600 mg or 5 tablets of 200mg) dispensed 6 times the the cost per 24-week course of ribavirin presented in the submission is either $ (Section D) or $ (Section E).

6.30 The PBAC noted in the base case, those patients achieving SVR are assumed to be permanently cured of HCV and that risk of re-occurrence and re-infection could be explored in sensitivity analyses. The PBAC noted that reinfection rates following SVR are being documented increasingly. In a study by Martin et al (AIDS, 2013; 27: 2551, doi: 10.109) of HIV+ MSM, among 145 individuals with a documented primary infection of HCV, the re-infection rate was 8.0 per 100 person-years (95% CI 5.7-11.3) overall and 9.6/100 person-years (95% CI 6.6-14.1) among those successfully treated. In a cohort of 119 inmates who had achieved SVR after completing therapy (81% of whom had a history of injection drug use), there was an overall re-infection rate of 5.27 cases per 100 person-years (Marco et al, J Hepatol. 2013, 59:45-51, doi: 10.1016/j). Thirdly, Grady et al (Clin Infect Dis 2013, 57 (S2):S105) observed that following treatment among people who inject drugs, the rate of HCV re-infection was 4.7 per 100 person-years (95% CI 1.9-11.2).

6.31 The PBAC recalled that in the consideration of the submissions for boceprevir and telaprevir that the ICER accepted by the PBAC was in the range of $15,000- $45,000 per QALY.

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

Estimated PBS usage & financial implications

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

6.33 The estimated PBS usage and financial implications are presented in the table below.

Summary of utilisation and financial estimates in the submission (base case)

	Y1*	Y2	Y3	Y4	Y5
Estimated eligible patient population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated patients (without sofosbuvir listed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients treated with any HCV drug (if sofusbuvir listed)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients treated with sofosbuvir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated cost to the PBS of listing	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated changes in use and cost of other drugs	[redacted]$[redacted]	[redacted]$[redacted]	[redacted]$[redacted]	[redacted]$[redacted]	[redacted]$[redacted]
Net financial impact of listing on the PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for government health budgets	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

*Note that submission's Year 1 estimate assumes [redacted] This underestimates total expenditure in Year 1, and

consequently the total cost across the first five years of listing. The preferred approach is to estimate use for full years, which can be apportioned once the date of listing is known.

6.34 The DUSC considered that there is very high potential for sofosbuvir to be used in an interferon free regimen due to patient preference. Interferon free regimens are approximately twice the cost of interferon containing regimens. In sensitivity analysis presented in the submission, varying the proportion of HCV genotype 3 treatment naïve interferon eligible patients accessing interferon-free regimens from [redacted]% to [redacted]% results in an approximate [redacted] increase in the net cost to the PBS. The DUSC requested that further sensitivity analyses be undertaken to assess the impact of all genotype 1 and 3 patients being treated with interferon free regimens (see below, SA 1). With all other parameters remaining as per the submission, this estimate doubles the net cost to the PBS.

6.35 The DUSC considered the predicted uptake of sofosbuvir, if used with interferon in genotype 1 patients (50% of the direct acting anti-viral market), is a likely underestimate. There will be little role for telaprevir and boceprevir with the availability of sofosbuvir due to the much shorter duration of treatment with interferon (12 weeks with sofosbuvir versus 24-48 weeks with telaprevir or boceprevir). The DUSC noted that simeprevir (Item 5.16) may still require a longer course of treatment with interferon than sofosbuvir regimens. A sensitivity analysis increasing the market share of sofosbuvir in genotype 1 interferon suitable patients to 100% (see below, SA 2) results in an approximate 20% increase in the total cost for sofosbuvir regimens, and an approximate 11% increase in the total net cost to the PBS (noting that genotype 1 patients comprise approximately 50% of the treated population)

One way sensitivity analyses requested by DUSC

Base case						
	Y1	Y2	Y3	Y4	Y5	Total
Patients treated with any HCV drug (if sofusbuvir listed)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of sofosbuvir to R/PBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R/PBS cost offsets	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost of R/PBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA 1 – all patients treated with interferon free regimens						
Patients treated with any HCV drug (if sofusbuvir listed)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug regimen cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Offsets	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA 2 – sofosbuvir uptake 100% for genotype 1 patients						
Patients treated with any HCV drug (if sofusbuvir listed)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug regimen cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Offsets	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.36 The submission expects an increase in the total number of patients treated with the listing of sofosbuvir. This is because there will be a larger eligible population and because of increased clinician capacity to treat a larger volume of patients due to shorter durations of treatment and reduced monitoring requirements. Based on

expert advice, the submission proposes that the size of the population will increase to [redacted]% of its current size in the first year of sofosbuvir's availability, followed by an additional [redacted]%, [redacted]%[redacted]% and [redacted]% in each subsequent year. The DUSC considered that this may possibly be an underestimate, particularly if there is an increase in the number of GPs treating hepatitis C as a result of the shorter and less toxic regimens. Further, the Stakeholder meeting (25 February 2014) stated that 'once the new all oral therapies are available it may be reasonable to expect that 10,000-15,000 patients to be treated in the next 3 to 4 years'. However the DUSC noted that if sofosbuvir is listed as requested in the submission, 'all-oral' regimens would not yet be available for most patients. There are approximately 230,000 people in Australia with chronic hepatitis C infection. The DUSC estimated that it would cost approximately in excess of $10 billion to treat all cases according to the requested restriction and assumptions (including market share) in the submission. This cost would increase further if more people than predicted are treated with interferon free regimens. The DUSC noted that not all people would present for treatment, be suitable for treatment, or be able to be treated due to capacity constraints. For example approximately 80,000 patients may be considered to be currently active in illicit drug-injecting behaviours and therefore at risk of re-infection and not suitable for treatment; and even if capacity increased from the current approximately 4,000 to 15,000 people treated per year (as per the Stakeholder meeting), it would take well over a decade to treat all infected people.

6.37 The DUSC also noted that ribavirin is not listed on the PBS in a form that is not co-packaged with peginterferon. If sofosbuvir is listed on the PBS for the treatment of HCV without co-administered peginterferon, it is unclear how patients would access ribavirin. In the absence of PBS subsidised ribavirin, clinicians may have to prescribe the currently available combination products of peginterferon and ribavirin and discard the peginterferon. Such a practice would represent substantial wastage and would impact on the estimate of cost-effectiveness of sofosbuvir.

6.38 Overall, the DUSC considered that the current treatments and treatment capacity are well understood but that utilisation could vary substantially from that presented in the submission.

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

7 PBAC Outcome

7.1 The PBAC rejected the submission for Section 100 (Highly Specialised Drugs Program) Authority Required (STREAMLINED) listing for sofosbuvir for the treatment of chronic hepatitis C on the basis of unacceptably high and likely underestimated cost-effectiveness and the high and likely underestimated budget impact on the PBS.

7.2 The PBAC recognised that treatment of HCV can be curative, compared to other viral infections such as HIV and HBV. Sofosbuvir is the first oral direct acting antiviral agent (DAA) that can be used to treat HCV genotypes 1-6 and provides patients with the first interferon-free treatment option. These benefits of new treatments were highlighted by the large number of comments from patients, health care professionals and organisations.

7.3 The PBAC noted the issues raised about the proposed restriction during the evaluation and consideration by the ESC and the DUSC. The PBAC considered these issues should be addressed in any resubmission to the PBAC. In particular:

- Any new proposed restriction should allow sofosbuvir to be accessed by patients infected with all genotypes.
- The criteria for 'Patients unsuitable for treatment with interferon based therapy' to access interferon-free treatment regimens had not yet been defined. The PBAC noted the proposed definition by the sponsor in the PSCR and pre-PBAC response and agreed with the ESC and DUSC about the difficulty to implement a complex definition of 'unsuitable for interferon' in the restriction and if the definition is broadly interpreted in practice, there is the high likelihood of use beyond the requested restriction.
- The PBAC noted that ribavirin alone was not registered on the ARTG. The PBAC was concerned that patients may obtain a co-pack of peginterferon and ribavirin and discard the peginterferon.
- The PBAC noted that eligibility criteria based on stage of hepatic fibrosis was proposed by the ESC. However, the PBAC agreed with the sponsor that currently it is difficult to implement this approach.

7.4 The PBAC agreed with the ESC and the DUSC that consideration of new treatment options for HCV should be framed in the evolving treatment landscape where patients are most likely waiting for the availability of interferon-free regimens. The PBAC noted that the sponsor proposed to exclude IFN-unsuitable patients with genotype 1 disease from the restriction. The PBAC considered that on the contrary, IFN-free regimens were likely to become the standard treatment in the near future. As an example of the rapidly evolving treatment landscape, both telaprevir and boceprevir, each with PEG+RBV were recommended for use in Australia in 2012 and are now not recommended for the treatment of patients with HCV genotype 1 in the guidelines of the American Association for the Study of Liver Disease and the Infectious Disease Society of America. The PBAC noted that over 30 DAAs are in clinical development, including inhibitors of NS5A, NS5B and NS3/4A as well as host-targeting antivirals.

7.5 The submission proposed the current active treatments as the comparator for the treatment of different HCV genotypes. While appropriate in the context of patients seeking treatment, the PBAC considered that the appropriate comparator is no treatment in view of the broader context of infected individuals whose treatment preference is interferon-free therapies.

7.6 The PBAC considered that the comparative magnitude of the benefit (SVR) of sofosbuvir presented in the submission was uncertain due to reliance on the single arm trials, some of which involved a small number of patients. The PBAC agreed with ESC that the evidence provided in the submission was the best available as the development program of sofosbuvir has been based predominantly on single arm trials.

7.7 The PBAC noted sofosbuvir was well tolerated in the trials and had superior safety of compared to currently PBS-listed treatment.

7.8 Based on the comparator that the PBAC considered most appropriate, sofosbuvir had superior efficacy and inferior safety compared to no treatment.

7.9 The PBAC accepted the economic model, but considered that the model structure should include:

- Allowance for re-infection with HCV in the base case.

- The probability assumption of morbidity and mortality for cirrhotic and non-cirrhotic patients who achieve SVR that is appropriate to the CHC population rather than probability of the general population.

7.10 The PBAC recalled that 30 years was considered to be a reasonable extrapolation for models of HCV infection in the consideration of the submissions for boceprevir and telaprevir. Truncating the model for sofosbuvir to 30 years increased the ICER/QALY for each of the eleven population subgroups presented in the submission, for example $105,000 - $200,000 to $105,000 - 200,000/QALY in genotype 1, treatment naïve, and interferon unsuitable patients.

7.11 The PBAC noted the discussion about the model assumption of the proportion of patients with cirrhosis between ESC and the sponsor. The PBAC considered that [redacted]% as presented in the submission was high and not justified. The PBAC noted the pre-PBAC response proposed a percentage of [redacted]% rather than the range of [redacted]%-[redacted]% suggested by the ESC. The PBAC noted that the value of 20.8% was the based on CHC patients in the ACHOS study with 'Stage 4: probable or definite cirrhosis' in the subset of 446 patients (36% of the entire ACHOS cohort) with at least one liver biopsy record (Table 9 of ACHOS Report No. 1 March 2010). The ACHOS also reported in the entire cohort that 'A total of 14% of patients had a diagnosis of cirrhosis, with 7% diagnosed on the basis of liver biopsy and 7% on clinical grounds' (Table 8 of ACHOS Report No. 1 March 2010).' In the context of the broader population of individuals infected with HCV, the PBAC considered that it was reasonable to accept a value of 14%, as observed in the entire cohort of the ACHOS study. The PBAC noted that percentage of patients with cirrhosis in a population of high need of treatment may be different.

7.12 The PBAC noted that the ICERs presented in the submission and in additional analyses by the ESC and the sponsor varied greatly depending on the treatment group. The PBAC recalled that for the submissions for boceprevir and telaprevir the ICER range accepted was $15,000- $45,000/QALY. The PBAC considered that trying to value sofosbuvir with a weighted ICER/QALY was completely inappropriate when the ICER/QALY for some treatment groups was substantially higher than this range. The PBAC was also concerned that the weightings that underpin the weighted value for each treatment group, were uncertain due to the number of assumptions made about the proportion of patients with prior treatment/cirrhosis/IFN eligibility and genotype.

7.13 The PBAC considered that the ICER/QALY were high and uncertain in IFN-free regimens for treatment for genotype 1 and genotype 3, which the PBAC considered to be the most informative and most likely largest treatment groups for decision making in the broader context of HCV treatment.

7.14 The PBAC noted that submission estimated by listing sofosbuvir, the net cost to the PBS over 5 years was approximately in excess of $1 billion (base case). The PBAC agreed with the analysis by DUSC that financial estimates were underestimated because:

- There is very high potential for sofosbuvir to be used in an interferon free regimen due to patient preference.
  - varying the proportion of HCV genotype 3 treatment naïve interferon eligible patients accessing interferon-free regimens from [redacted]% to [redacted]% results in an approximate [redacted]% increase in cost compared to the base case
  - if all HCV genotype 1 and 3 patients were treated with interferon free regimens , the cost is double the base case.

- Predicted uptake of sofosbuvir even if used with interferon in genotype 1 patients (50% of the direct acting anti-viral market) was likely underestimated.
  - Varying the proportion to 100% of the market results in an approximate [redacted]% increase in cost compared to the base case.
- There is a large pool of prevalent cases of HCV infection, but only a small proportion is currently treated. The volume of patients treated in the future will depend on whether the shorter duration and claimed reduction in toxicity with sofosbuvir containing regimens will allow more patients to be treated within the existing capacity. Other factors that may increase capacity include changes to the models of delivery for hepatitis C treatment.
- That a practice of obtaining a co-pack of peginterferon and ribavirin and discarding the peginterferon for IFN-free treatment would represent substantial wastage and would impact on the estimate of cost-effectiveness of sofosbuvir patients.

7.15 The PBAC considered, as the clinical management of individuals with HCV is moving so rapidly, that a broader Government and community approach is needed to maximise clinical outcomes and patient access to treatment. As well as subsidising new treatment on the PBS, other factors that increase the capacity to treat patients need to be explored.

7.16 The PBAC noted that the submission stated that there are advantages associated with the use of sofosbuvir for the treatment of prison inmates with HCV. The PBAC agreed but noted that there would logistical concerns such as frequent appointments with a specialist clinic and that inmates are routinely involved in high-risk behaviours and would be at a high risk of re-infection. The PBAC considered that the cost-effectiveness of sofosbuvir in this context would need to be established.

7.17 The TSANZ/ALA corresponded with the PBAC about patients with a high clinical need for treatment, namely patients with HCV infection who are awaiting a liver transplant or have cirrhosis complicated by severe portal hypertension. The PBAC recognised that interferon-free treatment options are required for this high need population, where interferon based treatments are contraindicated because side effects may precipitate hepatic decompensation. The PBAC noted the reporting of clinical trial data of patients treated pre-transplant remaining HCV RNA negative 12 weeks after liver transplant in the TSANZ/ALA proposal and the draft PI provided with the submission. Though clinical evidence is emerging of the benefit to these patient populations with treatment with interferon-free regimens, the comparative clinical benefit had not been presented to the committee and cost-effectiveness had not been established. A major resubmission for IFN-free treatment for patients with greatest clinical need, such as HCV complicated by cirrhosis and portal hypertension (platelets < 100,000 and serum albumin < 35 G/l) and in decompensated patients awaiting liver transplant may be an early step towards a broader access to a treatment for Australians with HCV infection.

7.18 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

8 Context for Decision

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

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

9 Sponsor's Comment

The sponsor had no comment.