

**7.04 SOFOSBUVIR
400mg, tablet;
Sovaldi®; Gilead Sciences Pty Ltd.**

1 Purpose of Application

1.1 The re-submission requested a Section 100 (Highly Specialised Drug Program), Authority Required (STREAMLINED) listing for sofosbuvir for the treatment of chronic hepatitis C (CHC) in the treatment-naïve genotype 1-6 and treatment-experienced genotype 2-3 patients. The first submission was considered by the PBAC in July 2014.

2 Requested listing

Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Genotypes 1, 3, 4, 5 or 6 Hepatitis C virus (HCV) infection treatment naïve patients

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
SOFOBUVIR Tablet 400mg	28	2	Sovaldi	Gilead Sciences Pty Ltd

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	<i>Chronic genotype 1, 3, 4, 5 or 6 hepatitis C infection</i>
PBS Indication	<i>Chronic genotype 1, 3, 4, 5 or 6 hepatitis C infection</i>
Restriction Level/ Method	<input type="checkbox"/> Restricted benefit <input checked="" 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 checked="" type="checkbox"/> Streamlined
Treatment criteria:	Must be treated in an accredited treatment centre.

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<p>Clinical criteria:</p>	<p><i>Patient must have compensated liver disease,</i></p> <p>AND</p> <p><i>Patient must not have received treatment with combinations of interferon alfa or peginterferon alfa or oral direct acting antiviral agents for hepatitis C C (with or without sofosbuvir or a protease inhibitor),</i></p> <p>AND</p> <p><i>The treatment must be in combination with peginterferon alfa and ribavirin only,</i></p> <p>AND</p> <p><i>The treatment must be limited to a maximum duration of 12 weeks.</i></p>
<p>Population criteria:</p>	<p><i>Patient must be an adult aged 18 years or older,</i></p> <p>AND</p> <p><i>Patient must not be breastfeeding. .</i></p>
<p>Prescriber Instructions</p>	<p><i>Evidence of chronic <i>genotype 1, 3, 4, 5 or 6</i> hepatitis C infection (repeatedly anti-HCV positive and HCV RNA positive) must be documented in the patient's medical records,</i></p> <p>AND</p> <p><i>A maximum of 2 repeats may be prescribed.</i></p> <p>AND</p> <p><i>Patients who have received prior treatment with an oral direct acting antiviral agent are not eligible to receive PBS-subsidised sofosbuvir, except where the patient has developed an intolerance to the other oral direct acting antiviral agents of a severity necessitating permanent treatment withdrawal. Details of the intolerance must be documented in the patient's medical records.</i></p>
<p>Administrative Advice</p>	<p><u>Note</u> <i>No increase in the maximum quantity or number of units may be authorised</i></p> <p><u>Note</u> <i>No increase in the maximum number of repeats may be authorised</i></p> <p><u>Note</u> Treatment centres are required to have access to the following appropriate specialist facilities for the provision of clinical support services for hepatitis C: (a) a nurse educator/counsellor for patients; and (b) 24-hour access by patients to medical advice; and (c) an established liver clinic</p>

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Genotype 2 treatment naïve patients (12 weeks)

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
SOFOSBUVIR Tablet 400mg	28	2	Sovaldi	Gilead Sciences Pty Ltd

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	<i>Chronic genotype 2 hepatitis C infection</i>
PBS Indication	<i>Chronic genotype 2 hepatitis C infection</i>
Restriction Level/ Method	<input type="checkbox"/> Restricted benefit <input checked="" 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 checked="" type="checkbox"/> Streamlined
Treatment criteria:	Must be treated in an accredited treatment centre.
Clinical criteria:	<i>Patient must have compensated liver disease,</i> AND <i>Patient must not have received prior treatment with combinations of interferon alfa or peginterferon alfa or oral direct acting antiviral agents (with or without sofosbuvir or a protease inhibitor) for hepatitis C</i> AND <i>The treatment must be in combination with ribavirin only,</i> AND <i>The treatment must be limited to a maximum duration of 12 weeks.</i>
Population criteria:	<i>Patient must be an adult aged 18 years or older,</i> AND <i>Patient must not be breastfeeding.</i>

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Prescriber Instructions	Evidence of <i>chronic genotype 2</i> hepatitis C infection (repeatedly anti-HCV positive and HCV RNA positive) must be documented in the patient's medical records, AND A maximum of 2 repeats may be prescribed. <i>Patients who have received prior treatment with an oral direct acting antiviral agent are not eligible to receive PBS-subsidised sofosbuvir, except where the patient has developed an intolerance to the other oral direct acting antiviral agents of a severity necessitating permanent treatment withdrawal. Details of the intolerance must be documented in the patient's medical records.</i>
Administrative Advice	<u>Note</u> <i>No increase in the maximum quantity or number of units may be authorised</i> <u>Note</u> <i>No increase in the maximum number of repeats may be authorised</i> <u>Note</u> Treatment centres are required to have access to the following appropriate specialist facilities for the provision of clinical support services for hepatitis C: (a) a nurse educator/counsellor for patients; and (b) 24-hour access by patients to medical advice; and (c) an established liver clinic

Genotype 3 treatment naïve patients-24 weeks treatment

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

* Special pricing arrangement

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	<i>Chronic genotype 3 hepatitis C infection</i>
PBS indication	<i>Chronic genotype 3 hepatitis C infection</i>
Restriction Level/ Method	<input type="checkbox"/> Restricted benefit <input checked="" 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 checked="" type="checkbox"/> Streamlined
Treatment criteria:	Must be treated in an accredited treatment centre.
Clinical criteria:	<i>Patient must have compensated liver disease,</i> AND <i>Patient must not have received prior treatment with combinations of interferon alfa or peginterferon alfa or oral direct acting antiviral agents-interferon alfa or peginterferon alfa (with or without sofosbuvir or a protease inhibitor) for hepatitis C,</i> AND <i>The treatment must be in combination with ribavirin only,</i> AND <i>The treatment must be limited to a maximum duration of 24 weeks.</i>
Population criteria:	<i>Patient must be an adult aged 18 years or older,</i> AND <i>Patient must not be breastfeeding.</i>

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<p>Prescriber Instructions</p>	<p>Evidence of chronic <i>genotype 3</i> hepatitis C infection (repeatedly anti-HCV positive and HCV RNA positive) must be documented in the patient's medical records,</p> <p>AND</p> <p>A maximum of 2 repeats may be prescribed. <i>Patients who have received prior treatment with an oral direct acting antiviral agent are not eligible to receive PBS-subsidised sofosbuvir, except where the patient has developed an intolerance to the other oral direct acting antiviral agents of a severity necessitating permanent treatment withdrawal. Details of the intolerance must be documented in the patient's medical records.</i></p>
<p>Administrative Advice</p>	<p><u>Note</u> <i>No increase in the maximum quantity or number of units may be authorised</i></p> <p><u>Note</u> <i>No increase in the maximum number of repeats may be authorised</i></p> <p><u>Note</u> Treatment centres are required to have access to the following appropriate specialist facilities for the provision of clinical support services for hepatitis C: (a) a nurse educator/counsellor for patients; and (b) 24-hour access by patients to medical advice; and (c) an established liver clinic</p>

Genotype 3 treatment experienced patients (12 weeks)

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
SOFOSBUVIR Tablet 400mg	28	2	Sovaldi	Gilead Sciences Pty Ltd

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	<i>Chronic genotype 3 hepatitis C infection</i>
PBS indication	<i>Chronic genotype 3 hepatitis C infection</i>
Restriction Level/ Method	<input type="checkbox"/> Restricted benefit <input checked="" 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 checked="" type="checkbox"/> Streamlined
Treatment criteria:	Must be treated in an accredited treatment centre.

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Clinical criteria:	<p>Patient must have compensated liver disease AND Patient must have received prior treatment with interferon alfa or peginterferon alfa for hepatitis C AND The treatment must be in combination with peginterferon alfa and ribavirin only. AND The treatment must be limited to a maximum duration of 12 weeks.</p>
Population criteria:	<p>Patient must be an adult aged 18 years or older AND Patient must not be breastfeeding</p>
Prescriber Instructions	<p>Evidence of <i>chronic genotype 3</i> hepatitis C infection (repeatedly anti-HCV positive and HCV RNA positive) must be documented in the patient's medical records, AND <i>Patients who have received prior treatment with an oral direct acting antiviral agent are not eligible to receive PBS-subsidised sofosbuvir, except where the patient has developed an intolerance to the other oral direct acting antiviral agents of a severity necessitating permanent treatment withdrawal. Details of the intolerance must be documented in the patient's medical records.</i></p>
Administrative Advice	<p><u>Note</u> <i>No increase in the maximum quantity or number of units may be authorised</i></p> <p><u>Note</u> <i>No increase in the maximum number of repeats may be authorised</i></p> <p><u>Note</u> Treatment centres are required to have access to the following appropriate specialist facilities for the provision of clinical support services for hepatitis C: (a) a nurse educator/counsellor for patients; and (b) 24-hour access by patients to medical advice; and (c) an established liver clinic</p>

Genotype 2 HCV infection treatment experienced patient (12 weeks)

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
SOFOSBUVIR Tablet 400mg	28	2	Sovaldi	Gilead Sciences Pty Ltd

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	<i>Chronic genotype 2 hepatitis C infection</i>

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PBS Indication:	<i>Chronic genotype 2 hepatitis C infection</i>
Restriction Level/Method	<input type="checkbox"/> Restricted benefit <input checked="" 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 checked="" type="checkbox"/> Streamlined
Treatment phase:	Initial treatment
Treatment criteria:	Must be treated in an accredited treatment centre.
Clinical criteria:	<p><i>Patient must have compensated liver disease,</i></p> <p>AND</p> <p>Patient must have received prior treatment with interferon alfa or peginterferon alfa for hepatitis C,</p> <p>AND</p> <p>The treatment must be in combination with ribavirin only,</p> <p>AND</p> <p>The treatment must be limited to a maximum duration of 12 weeks.</p>
Population criteria:	<p>Patient must be an adult <i>aged 18 years or older,</i></p> <p>AND</p> <p><i>Patient must not be breastfeeding</i></p>
Prescriber Instructions	<p>Evidence of chronic <i>genotype 2</i> hepatitis C infection (repeatedly anti-HCV positive and HCV RNA positive) must be documented in the patient's medical records,</p> <p>AND</p> <p><i>Patients who have received prior treatment with an oral direct acting antiviral agent are not eligible to receive PBS-subsidised sofosbuvir, except where the patient has developed an intolerance to the other oral direct acting antiviral agents of a severity necessitating permanent treatment withdrawal. Details of the intolerance must be documented in the patient's medical records.</i></p>

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Administrative Advice	<p><u>Note</u> No increase in the maximum quantity or number of units may be authorised</p> <p><u>Note</u> No increase in the maximum number of repeats may be authorised</p> <p><u>Note</u> Treatment centres are required to have access to the following appropriate specialist facilities for the provision of clinical support services for hepatitis C: (a) a nurse educator/counsellor for patients; and (b) 24-hour access by patients to medical advice; and (c) an established liver clinic</p>
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Genotype 3 HCV infection treatment experienced patient (24 weeks)

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
SOFOSBUVIR Tablet 400mg	28	2-5	Sovaldi	Gilead Sciences Pty Ltd

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	<i>Chronic genotype 3 hepatitis C infection</i>
PBS Indication:	<i>Chronic genotype 3 hepatitis C infection</i>
Restriction	<input type="checkbox"/> Restricted benefit <input checked="" 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 checked="" type="checkbox"/> Streamlined
Treatment phase:	Initial treatment
Treatment criteria:	Must be treated in an accredited treatment centre.
Clinical criteria:	<p>Patient must have received prior treatment with interferon alfa or peginterferon alfa for hepatitis C,</p> <p>AND</p> <p>The treatment must be in combination with ribavirin only,</p> <p>AND</p> <p>The treatment must be limited to a maximum duration of 24 weeks.</p>

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Population criteria:	<p>Patient must be an adult aged 18 years or older,</p> <p>AND</p> <p><i>Patient must not be breastfeeding</i></p>
Prescriber Instructions	<p>Evidence of chronic <i>genotype 3</i> hepatitis C infection (repeatedly anti-HCV positive and HCV RNA positive) must be documented in the patient's medical records,</p> <p>AND</p> <p>Patients who have received prior treatment with a sofosbuvir containing treatment regimen are not eligible to receive further PBS-subsidised sofosbuvir</p> <p><i>Patients who have received prior treatment with an oral direct acting antiviral agent are not eligible to receive PBS-subsidised sofosbuvir, except where the patient has developed an intolerance to the other oral direct acting antiviral agents of a severity necessitating permanent treatment withdrawal. Details of the intolerance must be documented in the patient's medical records.</i></p> <p>AND</p> <p>A maximum of 2 repeats may be prescribed.</p>
Administrative Advice	<p><u>Note</u> <i>No increase in the maximum quantity or number of units may be authorised</i></p> <p><u>Note</u> <i>No increase in the maximum number of repeats may be authorised</i></p> <p><u>Note</u> Treatment centres are required to have access to the following appropriate specialist facilities for the provision of clinical support services for hepatitis C: (a) a nurse educator/counsellor for patients; and (b) 24-hour access by patients to medical advice; and (c) an established liver clinic</p>

- 2.1 The re-submission reduced the requested dispensed price for maximum quantity (public hospital DPMQ) of sofosbuvir to \$██████, compared with \$██████ in the previous submission. Therefore, the cost of the sofosbuvir component of a 12-week course of treatment was \$██████. The re-submission also proposed that a rebate would apply under a special pricing arrangement to cap the cost of the sofosbuvir component of a 24-week course of treatment at \$██████.
- 2.2 A continuation listing for HCV genotype 3 patients was proposed in this re-submission, to cover the second 12 weeks supply of a 24-week course. The purpose of the continuation criterion was to allow a separate PBS Item number for the final 12 weeks of a 24-week course, and permits the proposed rebate to be applied to these prescriptions. Alternatively, the Secretariat proposed a single listing to supply the 24-week course.
- 2.3 Reference to the suitability for treatment with interferon was removed in the re-submission, enabling patients with genotype 3 HCV to opt for 24 weeks of treatment with sofosbuvir and ribavirin regardless of their eligibility for interferon. Given the

difficulty in determining 'interferon eligibility' in clinical practice, the Economic Sub-Committee (ESC) agreed that this change was appropriate.

- 2.4 The re-submission removed the request for a 24 week, interferon free regimen for patients with genotype 1 treatment-naïve HCV. The ESC agreed that this was appropriate, given that an interferon-free regimen of ledipasvir/sofosbuvir (LDV/SOF) was proposed by the sponsor for genotype 1 patients in another submission (considered at the March 2015 meeting) and patients would prefer to use interferon-free regimens. The ESC noted that if LDV/SOF was not approved, GT1 patients may wish to seek treatment with a 24 week, interferon free regimen.
- 2.5 The requirement for patients to have compensated liver disease had been removed from the proposed listing. The evidence presented in the submission, including the economic analysis, related only to those with compensated liver disease. The listing of other HCV therapies including PR and the PIs are limited to patients with compensated liver disease. The ESC considered that patients with decompensated liver disease are a subgroup with high clinical need. The ESC reflected on the poor tolerability of other IFN-containing regimens in this subgroup and considered that in the absence of evidence, effectiveness and cost-effectiveness was highly uncertain. However given the much better safety profile observed with IFN-sparing regimens, the ESC considered it reasonable to remove this requirement for SOF12 + RBV12 for GT2 patients and for SOF24 + RBV24 for GT3 patients.
- 2.6 The Drug Utilisation Sub-Committee (DUSC) noted that it is uncertain whether and when the current model of care involving specialist treatment centres will change to a greater role of primary care in HCV prescribing and monitoring, with a subsequent broader access to treatment.
- 2.7 The ESC noted that the submission assumed full compliance with the proposed treatment regimens. The ESC noted that post licensure reports from the United States and Europe suggest that adherence to treatment has been similar to that observed in the clinical trials, which had been conducted under controlled conditions. The ESC considered that if the treatment was provided outside specialist liver clinics, then there may be less follow up of patients potentially leading to lower SVR12 (sustained virologic response measured at 12 weeks).
- 2.8 The PBAC recalled the discussion at the Stakeholder meeting (New oral antivirals for the Treatment of Hepatitis C, February 2014) about the setting patients should be treated in. The PBAC considered that it was appropriate that the new all oral treatment regimens be listed in the General Schedule, to facilitated the longer term objectives for access to treatment, increase treatment rates and outcomes with a view to treat all patients with CHC over time.
- 2.9 General schedule listing is in line with initiatives such as The Fourth National Hepatitis C Strategy 2014-2017 and NSW Hepatitis C Strategy 2014-2020 to support a greater role of primary care in the prescribing and monitoring of the newer generation of antivirals, that have reduced side effects and more simplified dosing schedules. The PBAC noted that treatment of patients would initially remain in tertiary settings but expand as clinician experience grows.

- 2.10 The PBAC considered that that the Department, in consultation with clinical experts, should explore if primary care prescribing should be available to practitioners who have gained accreditation (as occurs currently for Section 100 prescribing) or in a Share Care Model (namely, in consultation with a clinician with experience of prescribing treatment for CHC, such as a hepatologist or infectious disease physician). The PBAC considered that an Authority Required listing was appropriate, but whether this Authority is written, telephone or streamlined remains to be finalised.

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

3 Background

- 3.1 Sofosbuvir was TGA registered on 30 June 2014 for the treatment of adults with CHC infection as a component of a combination antiviral treatment regimen.
- 3.2 This was the second submission for sofosbuvir to the PBAC. The first one was considered by the PBAC in July 2014 and rejected on the basis of an unacceptably high, and likely underestimated incremental cost-effectiveness ratio and the high and likely underestimated budget impact on the PBS (7.1, Item 5.17, July 2014 PBAC minutes).
- 3.3 Compared with the previous submission, the re-submission removed interferon (IFN) unsuitability from the requested listing, and for genotype 1 patients who were treatment-naïve, a treatment regimen of 24-week sofosbuvir and ribavirin (SOF24 + R24) was no longer requested, i.e. only SOF12 + PR12 was proposed. In its place, LDV/SOF was proposed in another submission as an IFN-free, ribavirin free and an oral treatment regimen for genotype 1 patients (both naïve and experienced) using LDV/SOF for 8 weeks or 12 weeks, depending on treatment history and cirrhotic state. For genotype 3 patients, the re-submission removed the IFN suitability requirement from the requested listing so that patients are allowed to opt for IFN-free treatment regimen of SOF24 + R24 regardless of their IFN suitability.
- 3.4 The re-submission updated the economic model based on the PBAC advice on the previous submission.

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 varices. Currently, HCV genotypes 1, 2 and 3 account for 49-55%, 5-8% and 33-42% of infections in Australia respectively.
- 4.2 Currently, the PBS reimburses direct acting antivirals (DAAs), including boceprevir, telaprevir and simeprevir (three HCV NS3/4A inhibitors, all of which are currently PBS listed to 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 and experienced patients with genotypes 2 or 3 HCV.
- 4.4 As noted earlier, IFN eligibility was removed from the requested listing in the re-submission. IFN-free treatment regimen (SOF24 + R24) was no longer requested for genotype 1 treatment-naïve patients. Genotype 3 patients had the option to use either an IFN-free treatment regimen (SOF24 + R24) or IFN-containing regimen (SOF12 + PR12). The ESC considered that most GT3 patients would seek an IFN-free treatment regimen.
- 4.5 The requested treatment regimens in the re-submission are summarised in the table below.

The proposed treatment regimens for patients with different genotypes

Genotype	Treatment duration	Treatment regimen
Treatment-naïve (no prior treatment with interferon)		
1, 4, 5, 6	12 weeks	SOF12 + PR12
2	12 weeks	SOF12 + R12
3	12 weeks	SOF12 + PR12
	24 weeks	SOF24 + R24
Treatment-experienced (prior therapy with an interferon based regimen)		
2	12 weeks	SOF12 + R12
3	12 weeks	SOF12 + PR12
	24 weeks	SOF24 + R24

SOF = sofosbuvir; PR = peginterferon and ribavirin; R = ribavirin
Source: Compiled during the evaluation

- 4.6 The ESC noted that international guidelines include recommended treatment of genotype 1 patients with a combination of sofosbuvir with simeprevir. Though the current wording of the listings would exclude such use, the ESC noted that patients could seek treatment for 12 to 24 weeks.

5 Comparator

- 5.1 The re-submission nominated currently available active treatments as the comparator for the treatment of different HCV genotypes. These were unchanged from the previous submission.
- 5.2 When considering the previous submission, the PBAC stated that, while the nominated comparator was appropriate in the context of patients seeking treatment, the appropriate comparator was 'no treatment' in view of the broader context of infected individuals whose treatment preference is interferon-free therapies (7.5, Item 5.17, July 2014 PBAC minutes). The ESC agreed that the most relevant comparator was no treatment.

- 5.3 The PBAC noted pre-PBAC response discussion on the comparator but reiterated that the most appropriate comparator was no 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 individuals (231), health care professionals (14) and organisations (18) via the Consumer Comments facility on the PBS website. The PBAC noted the correspondence from the Gastroenterological Society of Australia (GESA) on the use of DAAs in the treatment of patients with liver cirrhosis and severe portal hypertension, decompensated liver disease, or patients post liver transplant. The large number of comments and discussion highlighted the benefit of the availability of a highly effective treatment that should be made available for all infected individuals, the improved quality of life as well as the side effects avoided associated with the current treatments. The PBAC noted the patient preference for treatments with shorter durations, such 12 weeks compared to 24 weeks.
- 6.3 Representatives of the PBAC met with Hepatitis Australia, Hepatitis NSW, the Australian Injecting and the Illicit Drug User's League prior to the PBAC meeting, and reported the following key points to the PBAC in relation to the agenda items for the treatment of Hepatitis C :
- The high burden of disease associated with HCV infection was noted, and the urgent need for new treatments acknowledged. The significant adverse reactions associated with interferon-based therapies effectively eliminate these regimens as an option for some patients.
 - Concern about not having any treatment (the so-called "warehousing" practice adopted by clinicians), lack of access to transient elastography (including FibroScan[®]) and the lack of adequate follow-up for patients that are "warehoused" (i.e. where the patient is monitored but treatment is delayed). A complex referral system does not work for many groups of Hepatitis C patients – for example, it was quoted in the meeting that in the ACT only 28 patients have had access to treatment in the previous 12 months.
 - Community expectation with regard to the new drugs for Hepatitis C is high, and there is a high level of anticipation with patients keenly aware that these drugs are available in markets outside Australia. It was noted that these expectations were in place for a significant time before the sponsors chose to make reimbursement submissions to the PBAC.
 - Co-ordinated treatment of HCV, particularly moving towards the control (and potentially elimination) of the virus, would require health-system-wide approaches that are outside the remit of the PBAC.

- As the PBAC can recommend the circumstances under which PBS subsidy may be granted, elements such as whether to limit prescribing to specialists would be considered in potentially widening access. The PBAC particularly noted the advice of consumer groups that a PBS listing that limited access based on disease severity would not be supported. A listing that allowed broad access was favoured.
- It was also noted that representatives felt that these drugs should be assessed for their capacity for providing a cure within a 12 week period, not as longer term treatment strategies.

6.4 The PBAC noted and welcomed this input.

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

Clinical trials

6.5 The clinical evidence base remained unchanged from the previous submission (for more information see <http://pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2014-07/sofosbuvir-psd-07-2014>).

Trials and associated reports presented in the previous submission

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-	103	Single arm ^b , MC /	High	A phase 3, multicentre, randomised,	N Engl J Med

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Trial ID	N	Design/ duration ^a	Risk of bias ^c	Protocol title/ Publication title	Publication citation
0108 FUSION		24 weeks		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.	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 Zeuzem et al, Sofosbuvir and ribavirin in HCV Genotypes 2 and 3.	VALENCE Interim Synoptic CSR 08 October 2013 N Engl J Med 2014; 370:1993- 2001
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 submission, GT1)	157			an adaptive study, originally designed to investigate a range of regimens including the investigational agent GS-0938 with and without sofosbuvir and/or ribavirin. The study enrolled treatment naïve patients of all HCV genotypes, of	QUANTUM Abbreviated final CSR 10 July 2013

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Trial ID	N	Design/ duration ^a	Risk of bias ^c	Protocol title/ Publication title	Publication citation
				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-centre, 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	The Lancet, 2001: 958.

Trial ID	N	Design/ duration ^a	Risk of bias ^c	Protocol title/ Publication title	Publication citation
				of chronic hepatitis C: a randomised trial."	

^aDuration of trial is calculated as duration of treatment + required follow up to measure primary efficacy outcome.

^bFUSION 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.

^cOverall estimate of risk of bias includes bias associated with the nature of the comparison (i.e., a comparison of single arms from different trials has a high risk of bias).

^dSPRINT-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

Source: 6.5, Item 5.17, July 2014 PBAC minutes.

Comparative effectiveness

- 6.6 The key results of the SVR rates remained unchanged from the previous submission (for more information see <http://pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2014-07/sofosbuvir-psd-07-2014>).

Summary of comparative efficacy presented in the previous submission

GT	Treatment subgroup	Proposed	Comparator	Trial	SOF SVR	Comparator SVR	Extra SVRs /100
GT1	Naïve (N)	SOF12 + PR12	TVR/BOC + PR24/48	NEUTRINO Vs mixed	89%	55-75%	15 or 26
	N, IFN-free	SOF24 + R24	None	QUANTUM & SPARE (Sect C)	65%	0	65
GT2	Naïve	SOF12 + R12	PR24	FISSION	97%	78%	19
	Experienced (Exp)	SOF12 + R12	None	FUSION	31/36 =86%	0	86
GT3	Naïve	SOF12 + PR12	PR24	PROTON/ ELECTRON/ LONESTAR (Sect C) Vs FISSION(comp)	48/51 =94%	63%	34
	Exp	SOF12 + PR12	None	LONESTAR	20/24 =83%	0	83
GT3	N/Exp IFN-free	SOF24 + R24	None	VALENCE	98/105 =93% (N) to 113/145 =78% (Exp)	0	78-93
GT4-6	Naïve	SOF12 + PR12	PR48	NEUTRINO Vs	34/35 =97%	~50%	~47

GT	Treatment subgroup	Proposed	Comparator	Trial	SOF SVR	Comparator SVR	Extra SVRs /100
				Manns et al.			

Comparative harms

- 6.7 The key safety results remained unchanged from the previous submission (for more information see <http://pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2014-07/sofosbuvir-psd-07-2014>).

Summary of comparative safety presented in the previous submission

	Sofosbuvir	Comparator		Event rate/100 patients			Risk Difference (unadjusted) ^a	
				Sofosbuvir	Comparator		SOF vs BOC	SOF vs TVR
	NEUTRINO SOF12+PR12	SPRINT-2 BOC+PR28/48	ADVANCE TVR+PR24/48	SOF	BOC	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		-	

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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	-

Benefits/harms

6.8 The benefits/harms of sofosbuvir remained unchanged from the previous submission (for more information see <http://pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2014-07/sofosbuvir-psd-07-2014>).

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

Summary of benefits and harms presented in the previous submission

Patient group	comparison	Benefits/harms
Genotype 1, treatment-naïve, suitable for IFN	for every 100 patients treated with SOF12+PR12 in comparison to <u>BOC24+PR28/48 and TEL24+PR24/48</u>	<ul style="list-style-type: none"> • 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 <u>no treatment</u> (based on the NEUTRINO trial):	<ul style="list-style-type: none"> • 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

Patient group	comparison	Benefits/harms
Genotype 3, treatment-naïve, suitable for IFN	for every 100 patients treated with SOF12+PR12 in <u>comparison to PR24</u> :	<ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> 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 <u>no treatment</u> :	<ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> 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 3, treatment-naïve	On the basis of evidence presented by the submission, for every 100 patients treated with SOF24+R24 in comparison to <u>no treatment</u> (based on the VALENCE trial):	<ul style="list-style-type: none"> Approximately 93 additional patients would be expected to achieve SVR Comparative harms of the VALENCE trial was not presented in submission Based on the FISSION trial (SOF12+R12, including patients with Genotype 2 and 3), then: <ul style="list-style-type: none"> 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.

Source: 6.9, Item 5.17, July 2014 PBAC minutes and constructed during the evaluation.

Note: Since the previous sofosbuvir submission, simeprevir (a protease inhibitor) in combination with peginterferon and ribavirin has been listed for the treatment of patients with genotype 1 CHC. The PBAC considered that the [simeprevir] submission supported the claim that simeprevir is non-inferior in terms of comparative effectiveness (in achieving an SVR) and superior in terms of safety when compared with boceprevir and telaprevir (PSD – July 2014 PBAC meeting, 5.16 Simeprevir).

Clinical claim

- 6.9 The re-submission claimed that sofosbuvir has:
- Superior comparative effectiveness to peginterferon-containing active treatment and no treatment, and
 - Inferior comparative safety to no treatment, and
 - Superior comparative safety to peginterferon-containing active treatments.
- 6.10 At the July 2014 meeting, the PBAC considered that the comparative magnitude of the benefit (in terms of SVR) of sofosbuvir was uncertain due to reliance on single arm trials, some of which involved a small number of patients. The PBAC accepted that sofosbuvir had superior safety compared to currently PBS-listed treatment, and superior efficacy and inferior safety compared to no treatment (7.6, 7.7, 7.8, Item 5.17, July 2014 PBAC minutes).

- 6.11 The PBAC reiterated that the committee considered that the claim of superior comparative effectiveness and inferior comparative safety to no treatment was reasonably support by the data in the submission for GT1-GT6 treatment naïve and GT2-GT3 treatment experienced patients.

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

Economic analysis

- 6.12 The re-submission presented a modelled economic evaluation based on an unadjusted comparison of results from single arms of different studies that was similar to the previous submission. The evaluation was structured as a Markov state-transition model with nine health states, which described the progression of disease over the lifetime. The model captured both on-treatment and off-treatment phases.
- 6.13 The re-submission updated the model:
- To allow for re-infection (annual rate of 0.5% has been assumed);
 - To reduce the time horizon to 30 years (compared to 53 years in the previous submission);
 - To reduce the proportion of patients with cirrhosis to 14% (compared to 30% in the previous submission); and
 - To allow transition from the non-cirrhotic SVR health state to the cirrhosis health state (annual probability 0.5%) in a sensitivity analysis.
- 6.14 The executive summary of the re-submission claimed that the updated model had allowed a transition from cirrhotic patients who achieve SVR to decompensated cirrhosis, but this was not actually incorporated into the updated model. During the evaluation, this additional transition was explored in a sensitivity analysis.
- 6.15 The model structure and rationale are summarised in the table below.

Summary of model structure and rationale

Cohort size	10,000
Time horizon	30 years (revised from 53 years in the previous submission). This is consistent with PBAC advice (7.10 Item 5.17 PBAC Minutes, July 2014)
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

QALY = quality-adjusted life year; LYG = life year gained.

Source: compiled during the evaluation

- 6.16 Key drivers of the model are summarised in the table below.

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Key drivers of the model

Description	Method/Value	Impact
Morbidity and mortality of patients who achieve SVR	Model assumes no increased morbidity and mortality for cirrhotic and non-cirrhotic patients who achieve SVR in the base case. Sensitivity analyses were conducted by the re-submission and during the evaluation allowing a small possibility of disease progression from the respective SVR states. However, it is unclear if this is sufficient to capture increased morbidity and mortality of patients with SVR compared to the general population. The ESC considered that it was reasonable to expect that those non-cirrhotic patients who achieve SVR do not progress to cirrhosis, but it is unreasonable to assume that those with cirrhosis who achieve an SVR have no greater risk of hepatocellular carcinoma (for example) than the general population. It would be more reasonable to assume that they have a risk of morbidity and mortality which lies between the risk of the general population and cirrhotic patients who do not achieve SVR.	Moderate, favours sofosbuvir
Comparative SVR Rates	Based on an unadjusted single arm comparison. Concerns remain regarding the applicability of these results to the proposed population.	Moderate – High, unclear
Utility increment as a result of obtaining SVR	This value was consistent with the utility increment related to SVR applied in other economic evaluations of CHC infection. However, given the large incremental difference in SVR between sofosbuvir regimens and no treatment (assumed to be 0%), this assumption had a substantial impact.	Moderate, favours sofosbuvir

SVR = sustained virologic response; CHC = chronic hepatitis C

Source: compiled during the evaluation

The results of economic evaluation are summarised in the table below. The ICER for non-cirrhotic patients compared to no treatment ranged from \$45,000/QALY – \$75,000/QALY and for cirrhotic patients, \$15,000/QALY - \$45,000/QALY.

Results of the economic evaluation

Genotype	SOF regimen	Comparator	ICER (Cost/QALY)		
			Base case	Non-cirrhotic	Cirrhotic
Treatment-naïve					
Interferon eligible					
GT1	SOF12 + PR12	BOC + PR (24-48)	\$	\$	\$
		TVR+ PR (24-48)	\$	\$	\$
		LDV/SOF (8/12)*	SOF12+PR12 dominated		
		No Treatment	SOF12+PR12 costs less, but less effective		
GT2	SOF12 + R12	PR24	\$	\$	\$
		No treatment	\$	\$	\$
GT3	SOF24 + R24	PR24	\$	\$	\$
		No Treatment	\$	\$	\$
	SOF12 + PR12	PR24	\$	\$	\$
		No Treatment	\$	\$	\$
GT 4, 5, 6	SOF12 + PR12	PR48	\$	\$	\$
		No Treatment	\$	\$	\$
Interferon unsuitable					
GT2	SOF12 + R12	No Treatment	\$	\$	\$
GT3	SOF24 + R24	No Treatment	\$	\$	\$
Treatment-experienced					
Interferon eligible					
GT2	SOF12 + R12	No Treatment	\$	\$	\$
GT3	SOF24 + R24	No Treatment	\$	\$	\$
	SOF12 + PR12		\$	\$	\$
Interferon unsuitable					
GT2	SOF12 + R12	No Treatment	\$	\$	\$
GT3	SOF24 + R24	No Treatment	\$	\$	\$

GT = genotype; SOF = sofosbuvir; PR = peginterferon and ribavirin; R = ribavirin; BOC = boceprevir; TVR = telaprevir; LDV/SOF = ledipasvir/sofosbuvir.

*The proposed treatment duration for LDV/SOF is 8 weeks for non-cirrhotic patients and 12 weeks for those with cirrhosis.

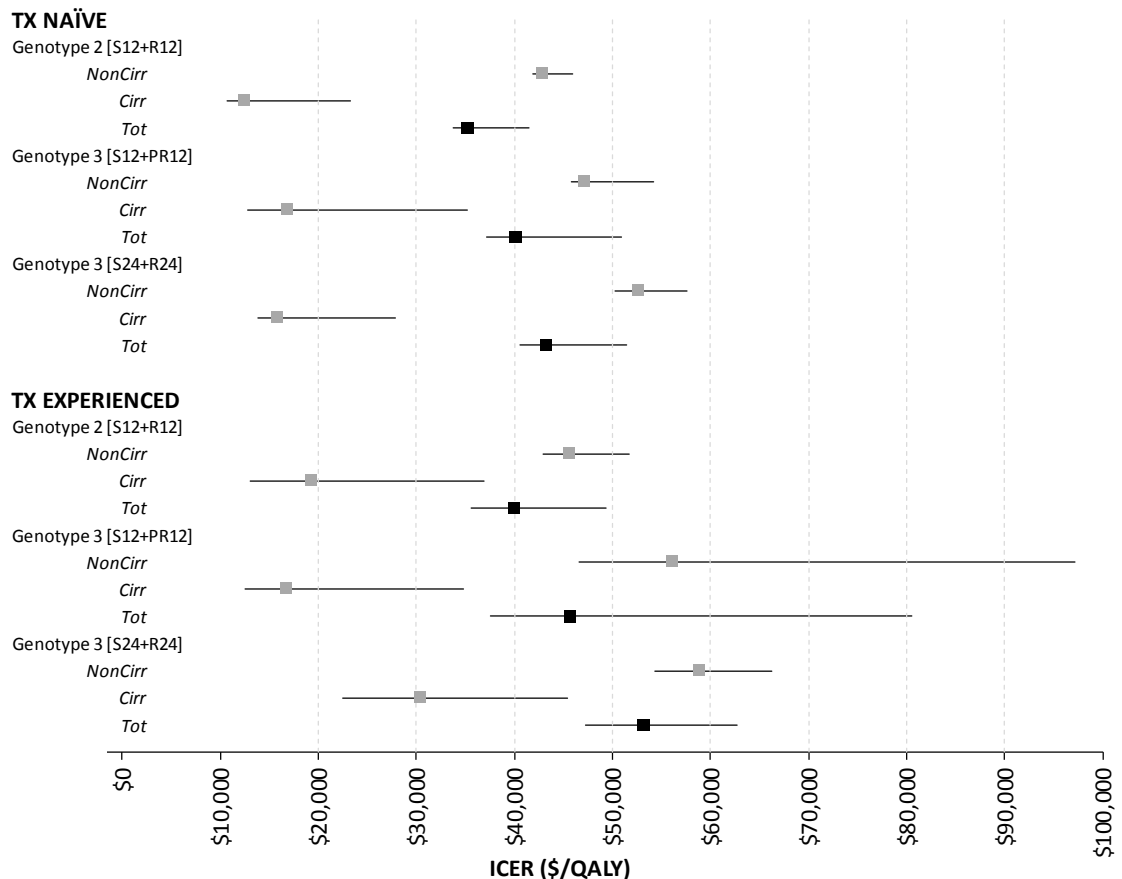
Source: compiled during the evaluation from 'Section D Workbook (Gilead SOF CEA model Nov 2014.xlsm)'.

- 6.17 Although the proposed listing in the re-submission had removed the interferon eligibility from the requested restriction, the updated model still separated the population into interferon eligible and interferon unsuitable. For genotype 2 patients (both naïve and experienced) there was a difference in the SVR rates applied between interferon eligible and interferon unsuitable patients and a difference in the disutility associated with the same treatment regimen (SOF12+R12). The same SVR was used for genotype 3 patients regardless of interferon suitability; however, there were small differences in the disutility associated with the same treatment regimen (SOF24+R24) depending on interferon suitability. As highlighted in the previous evaluation, the source and method by which these disutility estimates were derived remain uncertain, although these differences do not substantially impact the ICER. Neither the discrepancy in the SVR rates nor disutilities substantially affect the

difference in incremental cost effectiveness ratios (ICERs) between populations who were eligible and those who were unsuitable for interferon therapies.

- 6.18 The re-submission also presented a weighted incremental cost-effectiveness ratio of sofosbuvir and ledipasvir/sofosbuvir treatment regimens. The PBAC considered that trying to value sofosbuvir with a weighed ICER/QALY was inappropriate when the ICER/QALY for some treatment groups was substantially higher than the ICER range accepted in the submissions for telaprevir and boceprevir (\$15,000 - \$45,000/QALY) (7.12, Item 5.17, July 2014 PBAC Minutes).
- 6.19 During the evaluation, additional sensitivity analyses were conducted to examine the impact of SVR rates on the ICERs and the results indicated that the model was most sensitive to the lower 95% confidence limit of SVR rate for genotype 3 treatment-experienced patients receiving SOF12+PR12. This wide confidence interval and consequent variation in ICERs were driven by the small sample size from LONESTAR-2 for non-cirrhotic patients (10/12 patients; 95% CI 51.6%, 97.9%).

Forrest plot of sensitivity analysis, using lower and upper 95% confidence intervals for SVR rates against no treatment for Genotype 2 and 3.



TX = treatment; S = sofosbuvir; R = ribavirin; PR = peginterferon and ribavirin; NonCirr = non-cirrhotic patients; Cirr = cirrhotic patients; Tot = total. Source: constructed during the evaluation

- 6.20 The redacted figure above is a Forrest plot of the sensitivity analysis on the impact of SVR on ICER for GT2 and 3.
- 6.21 An analysis was carried out to explore the regimen cost required to achieve an ICER in the range of \$15,000 to \$45,000/QALY (a range which includes the values considered for the recommended listing of telaprevir and boceprevir). The ESC noted the very large opportunity cost of the new medicines for the treatment Hepatitis C. The ESC considered that in this situation, it would be appropriate and necessary for the PBAC to expect that the ICERs that would define potentially acceptable cost-effectiveness should be at the lower end of the range previously accepted for interventions for this disease.
- 6.22 For simplification, the model was modified in the following ways:
- Incremental cost effectiveness ratios calculated against 'no treatment'.
 - Analysis restricted to genotype 1 and genotype 3 subgroups as they account for the majority of prevalent cases in Australia (91%).
 - Removal of costs associated with the management of adverse events
 - The removal of costs associated with on-treatment monitoring. While it is recognised that some on-treatment monitoring will be required with the new HCV treatments, it is unlikely that monitoring costs will vary substantially between all-oral regimens.
 - Removal of disutility associated with treatment.
- The only treatment-specific parameters in the model were:
- Treatment regimen cost.
 - SVR rates.
- 6.23 The ESC noted, for example, that to an achieve ICER of \$15,000/QALY - \$45,000/QALY at an SVR of 0.95, the total cost of treatment in patients without cirrhosis was \$15,000 - \$45,000.

Total regimen cost to achieve an ICER in the range of \$15000/QALY and \$45000/QALY for given SVR rates.

SVR Rate	Regimen cost required to achieve an ICER of:			
	\$15,000/QALY	\$25,000/QALY	\$35,000/QALY	\$45,000/QALY
Genotype 1 Non-cirrhotic				
0.8	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
0.85	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
0.9	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
0.95	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
1	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Genotype 3 Non-cirrhotic				
0.8	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
0.85	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
0.9	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
0.95	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
1	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Genotype 1 & 3 Cirrhotic				
0.8	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
0.85	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
0.9	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
0.95	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
1	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

- 6.24 The ESC made the following general comments about the direct-acting antivirals (DAA) for the treatment of Hepatitis C:
- The most appropriate scenario for decision-making in the Australian context was the treatment of patients infected with Genotype 1 and 3 hepatitis C virus compared to no treatment. This reiterated the view of the PBAC at the July 2014 Meeting. (Sofosbuvir PSD, July 2014). The ESC considered that the treatments (submitted to the PBAC March 2015 meeting) were clinically effective in providing a SVR12 against hepatitis C. The ESC also considered that over time GT1 and GT3 treatment naïve non-cirrhotic patients are likely to become the predominant treatment populations, and therefore ICERs for this group should be most influential for decision-making.
 - In the economic analysis, when 100% of treated patients were assumed to be cirrhotic, the ICER was lower than when 100% of treated patients were assumed to be non-cirrhotic. Despite a smaller treatment effect (i.e. a lower SVR), the ESC noted that this ICER difference was driven by the delay of outcomes such as decompensated cirrhosis, hepatocellular carcinoma and mortality which generally were more likely to occur, and to occur sooner, in an untreated cirrhotic population.
 - In the economic models, it was more reasonable to assume that a cirrhotic patient with a SVR still had cirrhotic disease, and therefore would likely have an on-going risk of complications and mortality closer to that of an untreated cirrhotic patient than

to that of the background population. On the other hand, a SVR in a patient without cirrhosis is likely to avoid liver complications and associated disease due to viral eradication.

- The listing of the new treatment for hepatitis C should not be restricted by stage of hepatic fibrosis. However in clinical practice, the ESC considered that higher risk patients, such as patients with cirrhosis, are likely to be treated sooner following listing of interferon-free treatments. The ESC noted preliminary data from the ongoing, longitudinal, observational HCV-TARGET study ([clinicaltrials.gov NCT01474811](http://clinicaltrials.gov/NCT01474811)) showed that 45-60% of patients treated with interferon-free regimens were cirrhotic. (http://www.natap.org/2014/AASLDEASL/AASLDEASL_01.htm). However, the ESC considered that with the availability of highly effective and well-tolerated therapy, over time the predominant treatment population would be treatment naïve GT1 and GT3 patients without cirrhosis.
 - A consequence of this treatment pattern would be the rapid reduction of the pool of infected patients with cirrhosis. The ESC noted that all submissions assumed in the economic analysis that the proportion of patients with cirrhosis was greater than the figure of 5.9% (distribution of hepatic fibrosis stage F4) cited in the Recommendations from the Australian Liver Association (ALA). While the proportion of patients with cirrhosis would not reach zero, due to the current system capacity, the ESC considered that the assumption of a static and high prevalence of cirrhotic patients in the analysis favours the treatment arm in the medium to long term, and does not reflect the cost-effectiveness of overall treatment in the short term following the listing of these treatments. The ESC considered that it was more informative to present the ICER for non-cirrhotic and cirrhotic patients separately to see the extremes of the cost-effectiveness.
 - During the discussion, the ESC recalled the consideration of sofosbuvir at the July PBAC 2014 meeting. The ESC noted that the PBAC recalled that for the submissions for boceprevir and telaprevir the ICER range accepted was \$15,000- \$45,000/QALY. The PBAC considered that trying to value sofosbuvir with a weighted ICER was inappropriate when the ICER for some treatment groups was substantially higher than this range. The PBAC was also concerned that the weightings that underpin the weighted value for each treatment group, were uncertain due to the number of assumptions made about the proportion of patients with prior treatment/cirrhosis/IFN eligibility and genotype. (PSD, July 2014). In addition, the ESC noted that a weighted ICER should be generated by weighting costs and weighting benefits, before calculating the ratio.
 - The ESC noted the very large opportunity cost of the new medicines for the treatment Hepatitis C, if listed at the price proposed. A consequence of a significant opportunity cost to the health care system is the potential for reduced access to future cost-effective medicines. The ESC considered that in this situation, it would be appropriate and necessary for the PBAC to expect that the ICERs that would define potentially acceptable cost-effectiveness should be at the lower end of the range previously accepted for interventions for this disease.
- 6.25 The PBAC reiterated the view that trying to value a treatment with a weighted ICER was inappropriate when the ICERs for some treatment groups were substantially higher than the accepted cost-effectiveness ratio range.

- 6.26 The PBAC recalled that for the submissions for boceprevir and telaprevir the ICER range presented for a time horizon of 30 years was \$15,000/QALY - \$45,000/QALY. The PBAC noted, though the prevalent CHC population was approximately 230 000 patients, that approximately 60 000 patients could be treated within the estimated health system capacity over 5 years. The PBAC noted that the treatment of this proportion of the prevalent population of patients would represent a high opportunity cost to the health care system. The PBAC recalled that the threshold of incremental QALYs gained for treatments with large patient populations, such as population preventative interventions including lipid-lowering, anti-hypertensive drugs and vaccines was at the lower end of the ICER range that PBAC has accepted because these treatments typically have a high opportunity cost. Though not completely analogous to the vaccination program such as against Human Papillomavirus (HPV), the PBAC considered that subsidisation of CHC treatment, like the HPV vaccine, would provide both direct benefits to the treated individual and wider benefits to society with reductions in subsequent diseases such as CHC-related cancer and reduction in the prevalence of infection over time (as modelled in the publication by Sievert et al, 2014). The PBAC noted that the ESC Advice stated 'as in the consideration of all medicines with a potential high financial impact, there is a significant opportunity cost to the health care system, such as the access to future cost-effective medicines'. The PBAC considered that the acceptable ICER/QALY for Hepatitis C treatment should be at the low end of the range previously accepted for these other population preventative interventions because of the extraordinarily large opportunity cost associated with the treatment of CHC.
- 6.27 The PBAC considered that a price reduction for the cost of the entire treatment course would be required to give an ICER no greater than \$15,000/QALY based on the model presented in the SOF submission. The PBAC noted the small proportion of all patients with CHC that had cirrhotic disease (approximately 6%, advice from the ALA). The PBAC considered that the most appropriate scenario to determine the cost of a treatment would be based on the largest groups of the total prevalent population, namely treatment naïve non-cirrhotic Genotype 1 patients treated with LDV/SOF 8 weeks as a proxy for all Genotype 1 patients and treatment naïve non-cirrhotic Genotype 3 patients (weighing less than 75kg) treated with SOF+ RBV 24 weeks as a proxy for all Genotype 3, 2, 4, 5 and 6 patients. This cost of the entire treatment course should include the wholesale and pharmacy mark ups and dispensing fees associated with a General Schedule listing. The PBAC noted that the submission proposed a Genotype 3 treatment course of SOF+ PR12 and SOF+R24. The PBAC noted that the ESC and DUSC considered it more reasonable to assume that 100% of eligible patients would seek IFN-free treatment with SOF+R24. The PBAC agreed with this estimate but were unsure of the extent of uptake by eligible patients. The PBAC recommended that the cost to achieve a SVR12 should be independent of the treatment duration (such as 12 week or 24 weeks) considered to be appropriate to achieve a SVR in patients

Drug cost/patient:

- 6.28 12 week regimen: \$ [REDACTED] (compared to \$ [REDACTED] in the previous submission, representing a 15.7% price reduction), excluding cost of peginterferon + ribavirin; and

6.29 24 week regimen: \$ [REDACTED] (compared to \$ [REDACTED] in the previous submission, representing a 52.8% price reduction), excluding cost of ribavirin.

Estimated PBS usage & financial implications

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

6.31 The following estimates of PBS usage and financial implications were presented in the re-submission, excluding Genotype 1 patients. At year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be more than \$100 million.

Estimated number of patients treated / year both with and without sofosbuvir

Treated population per HCV Genotype	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients treated with sofosbuvir					
Genotype 2, treatment-naïve	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Genotype 2, treatment-experienced	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Genotype 3, treatment-naïve	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Genotype 3, treatment-experienced	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Genotype 4,5 or 6, Treatment-naïve	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total number of patients treated with sofosbuvir	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Source: compiled from 'Section E workbook – sofosbuvir resubmission_Final.xlsm'.

Estimated financial implications for the PBS / RPBS excluding Genotype 1 patients

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of treated patients					
With SOF-based regimens (GT 2-6)					
Without SOF-based regimens (GT 2-6)					
Cost implications of PBS listing of SOF					
Cost of sofosbuvir	\$	\$	\$	\$	\$
Savings due to superseded tm	-\$	-\$	-\$	-\$	-\$
Total net cost	\$	\$	\$	\$	\$
PBS component	\$	\$	\$	\$	\$
RPBS component	\$	\$	\$	\$	\$

SOF = sofosbuvir; GT = genotype; tm = treatment.

Source: Commentary on the Main Submission, Table E.4.1 p73.

- 6.32 The DUSC considered the estimates to be underestimated. The re-submission's assumption of the maximum number of patients who could be treated of 10,000 – 50,000 per year was less than the estimate from the HCV stakeholder meeting (February 2014) of up to 10,000 – 50,000 per year with prescribing continuing through tertiary specialist settings.
- 6.33 The DUSC noted the net cost to Government is underestimated by excluding the genotype 1 population. The SOF+PR regimen is more expensive than the alternative ledipasvir+sofosbuvir (LED+SOF) regimen for this patient group, at the prices proposed in the submission. DUSC considered that it is likely that some patients with genotype 1 would receive SOF+PR in place of LED+SOF because of a possible intolerance to LED.
- 6.34 Taking account of the proposed drug prices, treatment targets in the Fourth National Hepatitis C Strategy and assuming that care continues to be delivered through specialist treatment centres, DUSC estimated the following number of patients of all genotypes would be treated over the first five years of listing at a net cost to the PBS/RPBS of approximately \$3 billion over five years.

Year 1	Year 2	Year 3	Year 4	Year 5
6,600	9,900	15,000	15,000	15,000

- 6.35 The PBAC noted the DUSC advice on the item. The PBAC was of the view that the DUSC estimates for patients likely to be treated were appropriate. At year 1, the estimated number of patients with any HCV genotype was less than 10,000 per year and the net cost to the PBS would be approximately more than \$100 million per year, if based on the cost per treatment considered cost-effective by the PBAC. At year 5, the estimated number of patients was 10,000 – 50,000 per year and the net cost to the PBS would be approximately more than \$100 million per year. Over 5 years, it is estimated that approximately 50,000 – 100,000 per year patients would be treated, and the net cost would be more than \$100 million per year. The PBAC noted that currently approximately \$87.5 million is spent on treatments for CHC, while, if the health system had the capacity, to treat all CHC patients over 5 years, the cost would be over \$5,000 million.

Quality Use of Medicines

- 6.36 Single agent ribavirin is not listed on the PBS. Ribavirin is only available co-packaged with peginterferon from the PBS. In the absence of PBS subsidised single agent ribavirin, clinicians may have to resort to prescribing the currently available combination products involving peginterferon and ribavirin and discarding the peginterferon. If a Genotype 3 patient received 12 weeks of SOF plus peginterferon with ribavirin and then discarded the peginterferon, they would be treated with a sub-optimal course of SOF12+ R12. In addition, such a practice would represent substantial wastage and would impact on the estimate of cost-effectiveness of sofosbuvir.

Financial Management – Special Pricing and Risk Sharing Arrangements

- 6.37 The re-submission proposed a rebate offered under a special pricing arrangement to cap the cost of sofosbuvir component of the 24-week treatment course to \$ [REDACTED] (for public hospital use).
- 6.38 The PBAC noted the estimates of patients being treated presented in the DUSC advice, based on treatment targets in the Fourth National Hepatitis C Strategy 2014-2017 and assuming that care continues to be delivered through specialist treatment centres. The PBAC noted initiatives to support a greater role of primary care in the prescribing. Though the magnitude of this uptake is unknown, the PBAC considered that it was reasonable to assume that the estimates from DUSC over the next 5 years would remain appropriate in the context of a General Schedule listing, given that treatment would initially continue in specialist treatment centres; and that the uptake by general practitioners to become accredited to manage HCV may be low as noted in the NSW Hepatitis C Strategy 2014-2020. The PBAC recommended a Risk Share Arrangement (RSA).
- 6.39 The PBAC recommended that the RSA should consist of a cap on expenditure, with a 100% rebate for budget certainty. The cap on expenditure should be based on the DUSC estimates. The PBAC considered that the advice received from the Australian Liver Association, namely Bruggmann et al. (2014), was the most appropriate the source of HCV genotype distribution in Australia. The Committee recommended that the Department negotiate RSAs based on DUSC estimates of the patient population and treatment course per patient for each medicine, in a manner that can be

implemented and managed by the Department. The PBAC emphasised the importance of ensuring that these arrangements can be implemented in a way that would manage the overall cost to the Commonwealth for these medicines. Currently, the sponsors of SOF, LDV/SOF, and other sponsors of HCV treatments used in combination with SOF would be part of such agreement.

7 PBAC Outcome

- 7.1 The PBAC recommended the Authority Required listing of sofosbuvir for the treatment of Genotype 2 CHC (when in combination with ribavirin, 12 weeks) and Genotype 3 CHC (when in combination with ribavirin, 24 weeks) on the basis of cost-effectiveness of the treatment over no treatment. The PBAC recommended the Authority Required listing of sofosbuvir (when in combination with peg-interferon and ribavirin, 12 weeks) for the treatment of Genotype 3, 4, 5 and 6 CHC on the basis of cost-effectiveness of the treatment over no treatment. The PBAC recommended the Authority Required listing of sofosbuvir (when in combination with peg-interferon and ribavirin, 12 weeks) for the treatment of Genotype 1 CHC on the basis of cost-effectiveness of the treatment over no treatment and non-inferior efficacy with Ledipasvir/Sofosbuvir.
- 7.2 The PBAC reiterated that the Committee recognised that new treatments of HCV resulted in high rates of sustained virological response, where the HCV virus could not be detected in the blood of patients 12 weeks after treatment commenced. The PBAC noted that the large number of comments and presentations from patients, health care professionals and organisations highlighted the benefits of the availability of new treatments, particularly IFN-free regimens.
- 7.3 The PBAC recalled the discussion at the Stakeholder meeting (February 2014) about the setting patients should be treated in. The PBAC considered that it was appropriate that the new all oral treatment to be listed in the General Schedule, to facilitated the longer term objectives for access to treatment, increase treatment rates and outcomes and acknowledging initiatives such as The Fourth National Hepatitis C Strategy 2014-2017 and NSW Hepatitis C Strategy 2014-2020 to support a greater role of primary care in the prescribing and monitoring of the newer generation of antivirals, that have reduced side effects and more simplified dosing schedules. The PBAC noted that treatment of patients would initially remain in tertiary settings but expand as clinician experience grows. The PBAC considered that that the Department, in consultation with clinical experts, should explore whether prescribing should be available to practitioners who have gained accreditation (as occurs currently for Section 100 prescribing) or in a Share Care Model (namely, in consultation with a clinician with experience of prescribing treatment for CHC, such as a hepatologist or infectious disease physician). The PBAC considered that an Authority Required listing was appropriate, but whether this Authority is written, telephone or streamlined remains to be finalised.
- 7.4 The submissions proposed the current active treatments as the comparator. The PBAC reiterated their view that the appropriate comparator, when the submission was lodged, was no treatment, in view of the broader context of infected individuals whose treatment preference is interferon-free therapies.

- 7.5 The PBAC considered that the comparative magnitude of the benefit (SVR12) of the treatment presented in the submission was uncertain due to the reliance on single arm trials, some of which involved small number of patients. The PBAC reiterated the view that the evidence provided in the submission was the best available as the development programs of DAA has been based predominately on single arm trials.
- 7.6 The PBAC reiterated that the committee considered that the claim of superior comparative effectiveness and inferior comparative safety to no treatment was reasonably support by the data in the submission for GT1-GT6 treatment naïve and GT2-GT3 treatment experienced patients.
- 7.7 The PBAC accepted the structure of the economic model presented in the submission and noted the ESC Advice on the economic model.
- 7.8 The PBAC noted the DUSC advice on the item. The PBAC accepted the estimates of patient numbers. At year 1, the estimated number of patients was 6,660 and the net cost to the PBS would be approximately more than \$100 million, if based on the cost per treatment considered cost-effective by the PBAC. At year 5, the estimated number of patients was 15,000 and the net cost to the PBS would be approximately more than \$100 million. Over 5 year, it is estimated that approximately 61,500 patients would be treated, and the net cost would be more than \$100 million.
- 7.9 The PBAC noted that as a single-sponsor combination treatment, ledipasvir/sofosbuvir (considered at the March 205 meeting) is likely to be the first treatment to be negotiated for listing on the PBS. The PBAC considered that it would be appropriate for sponsors of combinations containing all oral agents targeted against HCV proteins to split the price of a treatment course equally.
- 7.10 In accordance with subsection 101(3BA) of the National Health Act 1953, the PBAC advised that the Committee is of the opinion that, on the basis of the material available at the March 2015 meeting, sofosbuvir should not be treated as interchangeable with other recommended treatments of CHC on an individual patient basis.
- 7.11 The PBAC noted that suitability of prescribing sofosbuvir by nurse practitioners would depend on the final listing conditions of sofosbuvir. The PBAC were of a mind that in principle nurse practitioners prescribing was likely to be suitable in the context of a share care model.
- 7.12 The PBAC recommended that the Safety Net 20 Day Rule should not apply.
- 7.13 The PBAC noted the restrictions for peginterferon and ribarivin should be modified to allow use with sofosbuvir
- 7.14 The resubmission is not eligible for an Independent Review, because the PBAC made a positive recommendation
- 7.15 The PBAC acknowledged that there was a high clinical need for more effective and tolerable treatment for HCV. The PBAC noted that there is a large number (around 230,000) of patients with the chronic HCV who are untreated and that the utilisation

of existing listings was low as patients were contraindicated or unwilling to take interferon. Based on the prevalence of HCV and the financial estimate presented in the submission, the PBAC considered that there would be a significant opportunity cost to the Commonwealth of listing oral treatments as their uptake would be substantially higher than currently subsidised medicines. The PBAC reiterated its view that the clinical management of individuals with HCV is moving so rapidly that a broader Government and community approach is needed to maximise the clinical outcomes and patient access to treatment. As well as subsidising new treatment on the PBS, other factors that increase the capacity to treat patients need to be explored.

7.16 The PBAC wished to advise the Minister that:

- While interferon-free oral direct acting antiviral (DAA) agents provide safe and effective treatment options for patients with chronic Hepatitis C (CHC), there is a substantial opportunity cost associated with the potential listing of these medicines. The lower estimate of this opportunity cost is more than \$3 billion over 5 years, at the prices proposed in the submissions. Given this large opportunity cost, the cost of a course of treatment should be set irrespective of the duration, and that other pricing policies be considered.
- The impact of the new antivirals on patients currently infected has been modelled by Sievert et al. (2014). This modelling shows that the number of people with chronic hepatitis C (CHC) will be reduced by 60% in 2030 compared to the base case of current treatment. The assumptions in the model include up to 13,500 people (including all fibrosis stages) are treated annually by 2018 and the DAA agents are expected to have rates of sustained virologic response (measured at 12 weeks, SVR12) up to 90% for genotype 1 and 80% for genotype 3 by 2016. The analyses accounted for mortality but did not consider re-infection.
- Advice from the Australian Liver Association (ALA) indicated that of the estimated 233,000 people living with Hepatitis C virus (HCV), 193,000 patients have been diagnosed. Listing of oral DAA agents may increase public and clinician awareness of the disease potentially leading to increased testing and diagnosis.
- The DUSC analysis shows that approximately 60 000 patients would be treated over 5 years, based on treatment targets in the Fourth National Hepatitis C Strategy 2014-2017, together with the advice from the ALA and February 2014 Stakeholder meeting (New oral antivirals for the Treatment of Hepatitis C). However, it is not clear how many people living with CHC will seek treatment, particularly if patients have to be seen in specialist liver clinics or wait for a referral to a liver clinic. Prescribing is likely to continue to be delivered through specialist clinics in the short-term until clinicians in other settings have learned how to use the DAA agents. Patients may still be required to go through the hospital system as part of their clinical management, which could be a limiting factor to uptake.
- Given the very large opportunity cost, one option would be to restrict access to treatment to those with the highest clinical need. The PBAC considered that it was inappropriate to restrict access, given the likely benefit of the DAA agents across the full spectrum of patients with CHC, from those with early disease to those patients with existing liver cirrhosis and severe portal hypertension, decompensated liver disease, or patients post liver transplant. The benefits in terms of avoidance or delay of decompensated cirrhosis, hepatocellular carcinoma and morbidity are likely to be seen earlier in the most severely ill, but population benefits, such as reduction in

transmission of the disease, are likely to occur with wide access to treatment. This and other benefits may be also realised via other community-based programmes and strategies, such as those described in the Fourth National Hepatitis C Strategy 2014-2017.

- The high response (sustained virologic response measured at 12 weeks, SVR12) observed in the clinical trials may only be realised if the adherence of patients in Australia to treatment is similar to those in the clinical trials. While there is a patient preference for shorter treatments, and new shorter treatment regimens are currently being tested, for some patients, 24 weeks of treatment are necessary. Therefore it is critical that appropriate prescribing education be put in place to ensure that the benefits to the Australian community are maximised.
- The treatment landscape of HCV treatment is changing rapidly, as new DAA agents or new combinations of DAA agents become available and treatment guidelines are regularly updated. It is likely that new DAA agents will be produced over the next 2 to 3 years that may further increase treatment options.
- In this context, the current treatment for CHC, such as peginterferon and ribavirin alone and in combination with telaprevir, boceprevir or simeprevir, are no longer cost-effective as currently listed especially given the higher rate of adverse effects observed in clinical practice for some treatment combinations compared to those observed in the clinical trials. The Minister may wish to review the listing of these products. The PBAC advised the Department to bring this consideration to the attention of the sponsor of these products. The Commonwealth currently pay approximately \$87 million for these treatments.

Outcome:

Recommended

8 Recommended listing

- 8.1 Add new item:
Restriction to be finalised

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

The Sponsor had no comment.