

**5.13 LEDIPASVIR 90 MG / SOFOSBUVIR  
400mg fixed dose combination tablet;  
Harvoni®; Gilead Sciences Pty Ltd.**

**1 Purpose of Application**

1.1 The submission requested Section 100 (Highly Specialised Drug Program) Authority Required (STREAMLINED) listing for the fixed dose combination of ledipasvir/sofosbuvir (LDV/SOF) for treatment of patients infected with genotype 1 chronic hepatitis C (CHC), irrespective of previous treatment history. The drugs included in this fixed dose combination product are not currently PBS listed as monotherapies.

**2 Requested listing**

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

Genotype 1 treatment naïve patients with hepatic cirrhosis

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
LEDIPASVIR/SOFOSBUVIR Tablet 90mg/400mg	28	2	HARVONI®	Gilead Sciences Pty Ltd

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	Medical Practitioners
Condition:	<i>Chronic genotype 1 hepatitis C infection</i>
PBS Indication:	<i>Chronic genotype 1 hepatitis C infection</i>
Restriction Level / Method:	Authority Required - In Writing Authority Required - Telephone Streamlined
Treatment criteria:	Must be treated in an accredited treatment centre.

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<p><b>Clinical criteria:</b></p>	<p><i>Patient must have compensated liver disease,</i></p> <p><i>AND</i></p> <p><i>Patient must have hepatic cirrhosis</i></p> <p><i>AND</i></p> <p><i>Patient must not have received prior treatment with combinations of interferon alfa or peginterferon alfa or oral direct acting antiviral agents for hepatitis C (with or without a protease inhibitor),</i></p> <p><i>AND</i></p> <p><del><i>The treatment must be limited to a maximum duration of 8 weeks in patients without hepatic cirrhosis,</i></del></p> <p><i>OR</i></p> <p><del><i>The treatment must be limited to a maximum duration of 12 weeks in patients with hepatic cirrhosis.</i></del></p>
<p><b>Population criteria:</b></p>	<p><i>Patient must be an adult aged 18 years or older,</i></p> <p><i>AND</i></p> <p><i>Patient must not be breastfeeding</i></p>
<p><b>Prescriber Instructions</b></p>	<p>Evidence of chronic genotype 1 hepatitis C infection (repeatedly anti-HCV positive and HCV RNA positive) must be documented in the patient's medical records</p> <p><i>Patients who have received prior treatment with an oral direct acting antiviral agent are not eligible to receive PBS-subsidised ledipasvir/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><del><i>A maximum of 2 repeats may be prescribed.</i></del></p>
<p><b>Administrative Advice</b></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>

## 2. Genotype 1 treatment naïve patients without hepatic cirrhosis

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
LEDIPASVIR/SOFOSBUVIR Tablet 90mg/400mg	28	≥ 1	HARVONI®	Gilead Sciences Pty Ltd

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	Medical Practitioners
Condition:	<i>Chronic genotype 1 hepatitis C infection</i>
PBS Indication:	<i>Chronic genotype 1 hepatitis C infection</i>
Restriction Level / Method:	Authority Required - In Writing Authority Required - Telephone Streamlined
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><i>Patient must not have hepatic cirrhosis,</i></p> <p>AND</p> <p><i>Patient must not have received prior treatment with combinations of interferon alfa or peginterferon alfa or oral direct acting antiviral agents for hepatitis C (with or without a protease inhibitor),</i></p> <p>AND</p> <p><i>The treatment must be limited to a maximum duration of 8 weeks in patients without hepatic cirrhosis,</i></p> <p>OR</p> <p><i>The treatment must be limited to a maximum duration of 12 weeks in patients with hepatic cirrhosis.</i></p>
Population criteria:	<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>

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<p><b>Prescriber Instructions</b></p>	<p>Evidence of chronic genotype 1 hepatitis C infection (repeatedly anti-HCV positive and HCV RNA positive) must be documented in the patient's medical records</p> <p><i>Patients who have received prior treatment with an oral direct acting antiviral agent are not eligible to receive PBS-subsidised ledipasvir/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><b>A maximum of 2 repeats may be prescribed.</b></p>
<p><b>Administrative Advice</b></p>	<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>

3. Genotype 1 treatment experienced patients

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
LEDIPASVIR/SOFOSBUVIR Tablet 90mg/400mg	28	2	HARVONI® Gilead Sciences Pty Ltd

<b>Category / Program</b>	Section 100 – Highly Specialised Drugs Program
<b>Prescriber type:</b>	Medical Practitioners
<b>Condition:</b>	<i>Chronic genotype 1 hepatitis C infection</i>
<b>PBS Indication:</b>	<i>Chronic genotype 1 hepatitis C infection</i>
<b>Restriction Level / Method:</b>	Authority Required - In Writing Authority Required - Telephone Streamlined
<b>Treatment criteria:</b>	Must be treated in an accredited treatment centre.

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<p><b>Clinical criteria:</b></p>	<p><i>Patient must have compensated liver disease,</i></p> <p>AND</p> <p><i>Patient must have received prior <i>interferon alfa</i> or <i>peginterferon alfa</i> treatment for <i>hepatitis C</i> (with or without a protease inhibitor),</i></p> <p>AND</p> <p>The treatment must be limited to a maximum duration of 12 weeks</p>
<p><b>Population criteria:</b></p>	<p>Patient must be <del>an adult</del> <i>aged 18 years or older,</i></p> <p>AND</p> <p><i>Patient must not be breastfeeding</i></p>
<p><b>Prescriber Instructions</b></p>	<p>Evidence of chronic genotype 1 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><del>A maximum of 2 repeats may be prescribed.</del>  <i>Patients who have received prior treatment with an oral direct acting antiviral agent are not eligible to receive PBS-subsidised ledipasvir/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><b>Administrative Advice</b></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>

2.2 The proposed PBS listings were in line with the treatment durations and dosing proposed in the draft Product Information. The listing was not restricted to patients with compensated liver disease. No evidence for the effectiveness or cost-effectiveness of LDV/SOF in patients with decompensated liver disease, hepatocellular carcinoma or who are awaiting a liver transplant has been provided in the submission. The ESC noted that the submission proposed LDV/SOF 8 Week regimen for treatment-naïve non-cirrhotic patients and LDV/SOF 12 week regimen for treatment-naïve cirrhotic and treatment experienced non-cirrhotic and cirrhotic patients. The ESC considered that there is a risk of an extension of treatment from 8 weeks to 12 weeks among treatment naïve non-cirrhotic patients (the largest treatment group). As the submission was made under the TGA/PBAC Parallel

Process and the TGA indication is not known, the ESC noted that Food and Drug Administration (FDA) have recommended LDV/SOF regimens that differ from the proposed listing, specifically treatment-naïve non-cirrhotic patients treated with LDV/SOF 12 weeks and treatment-experienced cirrhotic patients treated with LDV/SOF 24 weeks. In addition, the ESC noted that there is evidence of the use of ribavirin with LDV/SOF<sup>a</sup>.

- 2.3 The PBAC noted that pre-PBAC response stated ‘the treatment duration outlined in the Clinical Evaluation Report received from the TGA, which is more informative of the Australian treatment context and PBS-listing includes
- For treatment-naïve patients without cirrhosis the recommended duration of treatment with LDV/SOF is 8 weeks.
  - For treatment-naïve patients with cirrhosis the recommended duration of treatment with LDV/SOF is 12 weeks.
  - For treatment experienced patients with or without cirrhosis the recommended duration of treatment with LDV/SOF is 24 weeks.’
- 2.4 The proposed PBS listings delineated treatment naïve from treatment experienced on the basis of having received treatment with an interferon based regimen. Theoretically, the listing permitted patients who have failed a LDV/SOF treatment (or other interferon free treatment regimen) to remain eligible for treatment with LDV/SOF. For the proposed treatment naïve listing, the definition of prior treatment could be expanded to include the use of any direct acting antiviral (e.g. LDV/SOF or SOF). For the proposed treatment experienced listing, no evidence was provided to support repeated use of sofosbuvir containing regimens. The treatment-experienced patients in the ION-2 trial were those who had failed peginterferon and ribavirin (PR) and protease inhibitors. With the currently available evidence, the ESC agreed that the prior use of sofosbuvir or oral direct acting antiviral agents could be excluded from the listing.
- 2.5 The maximum number of repeats in the proposed listing is 2 (permitting 12 weeks of treatment). The treatment criteria restricted non-cirrhotic, treatment naïve patients to 8 weeks of treatment. Separate listings for cirrhotic and non-cirrhotic patients may be more appropriate to ensure non-cirrhotic patients only receive 8 weeks of treatment. Some prescribers may treat non-cirrhotic patients for 12 weeks rather than 8 weeks given the US Food and Drug Administration (FDA) recommending the 12 week treatment duration, citing that the observed relapse rate was greater in the 8 week treatment arm than the 12 week treatment arm.
- 2.6 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.

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<sup>a</sup> M. Bourlière, J-P Bronowicki, V de Ledinghen, et al. Ledipasvir/Sofosbuvir Fixed Dose Combination is Safe and Efficacious in Cirrhotic Patients Who Have Previously Failed Protease-Inhibitor Based Triple Therapy. American Association for the Study of Liver Diseases (AASLD) Liver Meeting. Boston, November 7-12, 2014. Abstract LB-6.

- 2.7 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.
- 2.8 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. The conditions of the listing would also depend on the final registered Product Information.
- 2.9 Listing was sought on the basis that LDV/SOF is cost-effective compared with PR plus protease inhibitors or no treatment.

### **3 Background**

- 3.1 **TGA status at time of PBAC consideration:** The submission was made under the TGA/PBAC Parallel Process. The TGA delegate's overview was provided on 3<sup>rd</sup> March 2015, and the TGA submission is scheduled to be considered at the 10<sup>th</sup> April 2015 meeting of the Advisory Committee on Prescription Medicines (ACPM).
- 3.2 This is the first submission of LDV/SOF to the PBAC for the treatment of genotype 1 CHC.

### **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, genotype 1 accounts for 49-55% of infections in Australia.
- 4.2 Direct acting antivirals (DAAs), including boceprevir, telaprevir and simeprevir (three HCV NS3/4A inhibitors, all of which must be used in combination with PR) are currently reimbursed on the PBS for the treatment of HCV Genotype 1.
- 4.3 Ledipasvir is a HCV NS5A inhibitor, which regulates HCV replication, and displays inhibition against HCV genotypes 1a and 1b. Sofosbuvir is a pan-genotypic inhibitor of HCV NS5B RNA polymerase, essential for viral replication. The active metabolite of sofosbuvir is incorporated by HCV NS5B and acts as a chain terminator. The

submission indicated that ledipasvir has a low barrier to resistance but when given in combination with sofosbuvir, viral resistance is much less likely. Sofosbuvir and ledipasvir have complimentary antiviral activity and therefore sofosbuvir acts to prevent the emergence of NS5A class resistance.

- 4.4 A submission (from the same sponsor as LDV/SOF) requesting listing of sofosbuvir in combination with PR for the treatment of patients infected with genotype 1 CHC who are naïve to prior HCV treatment will be considered by the PBAC at the same meeting. LDV/SOF provides an interferon-free, all-oral treatment option for genotype 1 CHC patients, irrespective of their previous treatment history. If LDV/SOF is listed, SOF+PR will only likely be used in genotype 1 patients who are intolerant to LDV.

## **5 Comparator**

- 5.1 The submission nominated two comparators – a protease inhibitor (boceprevir, telaprevir or simeprevir) in combination with PR or no treatment. The PBAC considered that, in this instance, the appropriate comparator is ‘no treatment’ in view of the broader context of infected individuals whose treatment preference is interferon-free therapies (Public Summary Document, para 7.5, Item 5.17, PBAC meeting July 2014). There has been a growing view that treatment regimens containing peginterferon should be avoided if interferon-free regimens are available. The ESC agreed that the most relevant comparator was no treatment.
- 5.2 The PBAC noted pre-PBAC response’s discussion on the comparator but reiterated that the most appropriate comparator was 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 (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<sup>®</sup>) 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 There were no head-to-head comparisons of combination LDV/SOF with any of the proposed comparators. Three studies involving LDV/SOF, 2 studies involving boceprevir, 2 studies involving telaprevir and 3 studies involving simeprevir were identified.

6.6 Details of the studies presented in the submission are provided in the table below.

#### Studies and associated reports presented in the submission

Study ID	Protocol title/ Publication title	Publication citation
<b>Studies of LDV/SOF</b>		
ION-1 NCT01701401	A Phase 3, Multi-centre, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5885 Fixed-Dose	Final CSR 28 July 2014

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Study ID	Protocol title/ Publication title	Publication citation
Afdhal et al 2014	Combination ± Ribavirin for 12 and 24 Weeks in Treatment-Naive Subjects with Chronic Genotype 1 HCV Infection	
	Afdhal, N., S. Zeuzem, P. Kwo, M. Chojkier, N. Gitlin, M. Puoti, M. Romero-Gomez, <i>et al.</i> "Ledipasvir and Sofosbuvir for Untreated HCV Genotype 1 Infection."	<i>New England Journal of Medicine</i> 370, no. 20 (2014): 1889-98.
ION-2 NCT01768286 Afdhal et al 2014	A Phase 3, Multi-centre, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5885 Fixed-Dose Combination ± Ribavirin for 12 and 24 Weeks in Treatment-Experienced Subjects with Chronic Genotype 1 HCV Infection	Final CSR 9 June 2014
	Afdhal, N., K. R. Reddy, D. R. Nelson, E. Lawitz, S. C. Gordon, E. Schiff, R. Nahass, <i>et al.</i> "Ledipasvir and Sofosbuvir for Previously Treated HCV Genotype 1 Infection."	<i>New England Journal of Medicine</i> 370, no. 16 (2014): 1483-93.
ION-3 NCT01851330 Kowdley et al 2014	A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination ± Ribavirin for 8 Weeks and Sofosbuvir/Ledipasvir Fixed-Dose Combination for 12 Weeks in Treatment-Naive Subjects with Chronic Genotype 1 HCV Infection	Final CSR 16 June 2014
	Kowdley, K. V., S. C. Gordon, K. R. Reddy, L. Rossaro, D. E. Bernstein, E. Lawitz, M. L. Shiffman, <i>et al.</i> "Ledipasvir and Sofosbuvir for 8 or 12 Weeks for Chronic HCV without Cirrhosis."	<i>New England Journal of Medicine</i> 370, no. 20 (2014): 1879-88.
<b>Supplementary studies of protease inhibitor + peginterferon + ribavirin</b>		
SPRINT-2 (boceprevir) NCT00705432 Poordad et al 2011	<b>Primary publication</b> Poordad, F., J. McCone, Jr., B. R. Bacon, S. Bruno, M. P. Manns, M. S. Sulkowski, I. M. Jacobson, <i>et al.</i> "Boceprevir for Untreated Chronic HCV Genotype 1 Infection."	<i>N Engl J Med</i> 364, no. 13 (Mar 31 2011): 1195-206
	Gordon, S. C., E. M. Yoshida, E. J. Lawitz, B. R. Bacon, M. S. Sulkowski, M. Davis, F. Poordad, <i>et al.</i> "Adherence to Assigned Dosing Regimen and Sustained Virological Response among Chronic Hepatitis C Genotype 1 Patients Treated with Boceprevir Plus Peginterferon Alfa-2b/Ribavirin." <sup>6</sup>	<i>Aliment Pharmacol Ther</i> 38, no. 1 (Jul 2013): 16-27.
	Jacobson, I. M., P. Marcellin, S. Zeuzem, M. S. Sulkowski, R. Esteban, F. Poordad, S. Bruno, <i>et al.</i> "Refinement of Stopping Rules During Treatment of Hepatitis C Genotype 1 Infection with Boceprevir and Peginterferon/Ribavirin." <sup>7</sup>	<i>Hepatology</i> 56, no. 2 (Aug 2012): 567-75.
RESPOND-2 (boceprevir) NCT00708500 Bacon et al 2011	<b>Primary publication</b> Bacon, B. R., S. C. Gordon, E. Lawitz, P. Marcellin, J. M. Vierling, S. Zeuzem, F. Poordad, <i>et al.</i> "Boceprevir for Previously Treated Chronic HCV Genotype 1 Infection."	<i>N Engl J Med</i> 364, no. 13 (Mar 31 2011): 1207-17.
	Gordon, S. C., E. M. Yoshida, E. J. Lawitz, B. R. Bacon, M. S. Sulkowski, M. Davis, F. Poordad, <i>et al.</i> "Adherence to Assigned Dosing Regimen and Sustained Virological Response among Chronic Hepatitis C Genotype 1 Patients Treated with Boceprevir Plus Peginterferon Alfa-2b/Ribavirin." <sup>6</sup>	<i>Aliment Pharmacol Ther</i> 38, no. 1 (Jul 2013): 16-27.
	Jacobson, I. M., P. Marcellin, S. Zeuzem, M. S. Sulkowski, R. Esteban, F. Poordad, S. Bruno, <i>et al.</i> "Refinement of Stopping Rules During Treatment of Hepatitis C Genotype 1 Infection with Boceprevir and Peginterferon/Ribavirin." <sup>7</sup>	<i>Hepatology</i> 56, no. 2 (Aug 2012): 567-75.
	Barnard, R. J., J. A. Howe, R. A. Ogert, S. Zeuzem, F. Poordad, S. C. Gordon, R. Ralston, <i>et al.</i> "Analysis of Boceprevir Resistance Associated Amino Acid Variants (Ravs) in Two Phase 3 Boceprevir Clinical Studies." <sup>9</sup>	<i>Virology</i> 444, no. 1-2 (Sep 2013): 329-36.
Flamm et al 2013	Flamm, S. L., E. Lawitz, I. Jacobson, M. Bourliere, C. Hezode, J. M. Vierling, B. R. Bacon, <i>et al.</i> "Boceprevir with Peginterferon Alfa-2a-	<i>Clin Gastroenterol Hepatol</i> 11, no. 1 (Jan

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Study ID	Protocol title/ Publication title	Publication citation
(boceprevir) NCT00845065	Ribavirin Is Effective for Previously Treated Chronic Hepatitis C Genotype 1 Infection."	2013): 81-87 e4; quiz e5.
<b>ADVANCE</b> (telaprevir) NCT00627926 Jacobson et al 2011	<b>Primary publication</b> Jacobson, I. M., J. G. McHutchison, G. Dusheiko, A. M. Di Bisceglie, K. R. Reddy, N. H. Bzowej, P. Marcellin, <i>et al.</i> "Telaprevir for Previously Untreated Chronic Hepatitis C Virus Infection." Vera-Llonch, M., M. Martin, J. Aggarwal, M. Donepudi, M. Bayliss, T. Goss, and Z. Younossi. "Health-Related Quality of Life in Genotype 1 Treatment-Naive Chronic Hepatitis C Patients Receiving Telaprevir Combination Treatment in the Advance Study." <sup>12</sup>	<i>N Engl J Med</i> 364, no. 25 (Jun 23 2011): 2405-16. <i>Aliment Pharmacol Ther</i> 38, no. 2 (Jul 2013): 124-33.
<b>REALIZE</b> (telaprevir) NCT00703118 Zeuzem et al 2011	<b>Primary publication</b> Zeuzem, S., P. Andreone, S. Pol, E. Lawitz, M. Diago, S. Roberts, R. Focaccia, <i>et al.</i> "Telaprevir for Retreatment of HCV Infection." Pol, S., J. Aerssens, S. Zeuzem, P. Andreone, E. J. Lawitz, S. Roberts, Z. Younossi, <i>et al.</i> "Limited Impact of I128b Genotype on Response Rates in Telaprevir-Treated Patients with Prior Treatment Failure." <sup>14</sup> De Meyer, S., I. Dierynck, A. Ghys, M. Beumont, B. Daems, B. Van Baelen, J. C. Sullivan, <i>et al.</i> "Characterization of Telaprevir Treatment Outcomes and Resistance in Patients with Prior Treatment Failure: Results from the Realize Trial." <sup>15</sup> Zeuzem, Stefan, Ralph DeMasi, Alessandra Baldini, Bruce Coate, Donghan Luo, Joseph Mrus, and James Witek. "Risk Factors Predictive of Anemia Development During Telaprevir Plus Peginterferon/Ribavirin Therapy in Treatment-Experienced Patients." <sup>16</sup>	<i>N Engl J Med</i> 364, no. 25 (Jun 23 2011): 2417-28. <i>J Hepatol</i> 58, no. 5 (May 2013): 883-9. <i>Hepatology</i> 56, no. 6 (Dec 2012): 2106-15. <i>Journal of Hepatology</i> 60, no. 6 (2014): 1112-17.
<b>QUEST-1</b> (simeprevir) NCT01289782 Jacobson et al 2014	<b>Primary publication</b> Jacobson, I. M., G. J. Dore, G. R. Foster, M. W. Fried, M. Radu, V. V. Rafalsky, L. Moroz, <i>et al.</i> "Simeprevir with Pegylated Interferon Alfa 2a Plus Ribavirin in Treatment-Naive Patients with Chronic Hepatitis C Virus Genotype 1 Infection (Quest-1): A Phase 3, Randomised, Double-Blind, Placebo-Controlled Trial."	<i>Lancet</i> 384, no. 9941 (Aug 2 2014): 403-13.
<b>QUEST-2</b> (simeprevir) NCT01290679 Manns et al 2014	<b>Primary publication</b> Manns, M., P. Marcellin, F. Poordad, E. S. de Araujo, M. Buti, Y. Horsmans, E. Janczewska, <i>et al.</i> "Simeprevir with Pegylated Interferon Alfa 2a or 2b Plus Ribavirin in Treatment-Naive Patients with Chronic Hepatitis C Virus Genotype 1 Infection (Quest-2): A Randomised, Double-Blind, Placebo-Controlled Phase 3 Trial."	<i>Lancet</i> 384, no. 9941 (Aug 2 2014): 414-26.
<b>PROMISE</b> (simeprevir) NCT01281839 Forns et al 2014	<b>Primary publication</b> Forns, X., E. Lawitz, S. Zeuzem, E. Gane, J. P. Bronowicki, P. Andreone, A. Horban, <i>et al.</i> "Simeprevir with Peginterferon and Ribavirin Leads to High Rates of SVR in Patients with HCV Genotype 1 Who Relapsed after Previous Therapy: A Phase 3 Trial."	<i>Gastroenterology</i> 146, no. 7 (Jun 2014): 1669-79 e3.

Source: Table B-4, pp45-47 of the submission

All three LDV/SOF studies were Phase 3 randomised, open-label, multi-centre trials that compared different LDV/SOF±ribavirin (RBV) treatment arms of different durations in genotype 1 HCV patients. None of the studies included a relevant comparator. Therefore these studies were essentially single arm non-comparative studies for the purpose of the submission. The relevant trial arms and durations of treatment are summarised in the table, along with other key features.

**Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias <sup>a</sup>	Patient population	Outcome	Use in modelled evaluation
<b>Treatment-naïve</b>						
<b>LDV/SOF</b>						
ION-1 LDV/SOF 12 weeks	34	Single arm of R, OL / 12 weeks post treatment	High/unclear	Treatment-naïve cirrhotic	SVR12	used
ION-3 LDV/SOF 8 weeks	215	Single arm of R, OL / 12 weeks post treatment	High/unclear	Treatment-naïve, non-cirrhotic	SVR12	used
<b>Treatment-experienced</b>						
<b>LDV/SOF</b>						
ION-2 LDV/SOF 12 weeks	109	Single arm of R, OL / 12 weeks post treatment	High/unclear	Treatment-experienced (both non-cirrhotic and cirrhotic)	SVR12	used

<sup>a</sup> refers to bias associated with indirect comparison between LDV/SOF and each of active treatment or no treatment.

LDV/SOF = ledipasvir/sofosbuvir; R = randomised; OL = open label; SVR = sustained virologic response.

Source: compiled during the evaluation.

- 6.7 The comparison of LDV/SOF vs protease inhibitor + PR was performed by comparing single arms (or pooled results of single arms) from studies that lack a common comparator, without any discussion about the exchangeability of the study populations. Comparisons were therefore unadjusted and indirect. Overall, the risk of bias associated with such indirect comparisons was very high and resulted in substantial uncertainty in terms of the magnitude of any difference observed between trial arms.
- 6.8 The comparison of LDV/SOF vs no treatment, in terms of efficacy (sustained virologic response, SVR) was less likely to be biased, provided that the study populations were representative of the target PBS population. However, it was unclear whether the open label design of the studies would impact on the reported safety.

**Comparative effectiveness**

- 6.9 The SVR rates by study, and in the presence or absence of cirrhosis, are presented in the table below. Only the trial arms relevant to the proposed PBS listing are reproduced. SVR rates for cirrhotic and non-cirrhotic patients are presented separately when relevant to the proposed listing and when the data were available.

**Results of SVR rates in the included studies**

Trial	Regimen	Non-cirrhotic % (95%CI) <sup>a</sup>	Cirrhotic % (95%CI) <sup>a</sup>	Total population % (95%CI) <sup>a</sup>
<b>Treatment naïve</b>				
ION-1	LDV/SOF12		32/34 94.1% (80.3%, 99.3%)	
ION-3	LDV/SOF8	202/215 94% (89.9%, 96.7%)		
SPRINT-2 (ARM2)	BOC24+PR28-48 (RGT)	222/337 65.9% (60.5%, 70.9%)		
SPRINT-2 (ARM3)	BOC44+PR48		10/24 41.7% (22.1%, 63.4%)	
ADVANCE	TVR12PR24-48 (RGT)	258/342 75.4% (70.5%, 79.9%)	13/21 61.9% (38.4%, 81.9%)	271/363 74.7% (69.9%, 79.1%)
QUEST-1	SMV12+PR24-48 (RGT)	188/229 82.1% (76.5%, 86.8%)	18/31 58.1% (39.1%, 75.5%)	210/264 79.5% (74.2%, 84.2%)
QUEST-2	SMV12+PR24-48 (RGT)	189/231 81.8% (76.2%, 86.6%)	11/17 64.7% (38.3%, 85.8%)	209/257 81.3% (76%, 85.9%)
<b>Treatment experienced</b>				
ION-2	LDV/SOF12 <sup>b</sup>	83/87 95.4% (88.6%, 98.7%)	19/22 86.4% (65.1%, 97.1%)	102/109 93.6% (87.2%, 97.4%)
RESPOND-2 (GROUP2)	BOC32+PR36-48 (RGT)	85/132 64.4% (55.6%, 72.5%)		
RESPOND-2 (GROUP3)	BOC44+PR48 <sup>c</sup>	85/128 66.4% (57.5%, 74.5%)	17/22 77.3% (54.6%, 92.2%)	107/161 66.5% (58.6%, 73.7%)
FLAMM 2013	BOC44+PR48			86/134 64.2% (55.4%, 72.3%)
REALIZE	TVR12+PR48	94/134 70.1% (61.6%, 77.7%) <sup>d</sup>	77/132 58.3% (49.4%, 66.8%) <sup>d</sup>	171/266 64.3% (58.2%, 70%)
PROMISE	SMV12+PR24-48 (RGT)	169/211 80.1% (74.1%, 85.3%)	29/39 74.4% (57.9%, 87%)	206/260 79.2% (73.8%, 84%)

<sup>a</sup>95% confidence intervals have been calculated during the evaluation using the confidence interval command (ci) in Stata.

<sup>b</sup> The 24 week LDV/SOF arm achieved 100% (22/22) SVR rate in cirrhotic patients. The FDA has recommended 24 weeks of LDV/SOF for treatment experienced patients who have cirrhosis. The PBAC noted that the TGA evaluator has also recommended 24 weeks for treatment experienced patients.

<sup>c</sup> Some non-cirrhotic patients may be treated longer in this arm than would be treated according to the PBS listing (depending upon type of responder).

<sup>d</sup>NOTE: not presented by presence or absence of cirrhosis - figures are for F0-2 and F3-4. As such, the SVR rates are likely higher for both categories than had they been reported for cirrhotic vs non-cirrhotic.

SVR = sustained virologic response; LDV/SOF = ledipasvir/sofosbuvir; BOC = boceprevir; PR = peginterferon and ribavirin;

RGT = response guided therapy; TVR = telaprevir; SMV = simeprevir.

Source: in the submission, ION-1, Table B-52, pp116-117; ION-3, Table B-53, pp117-118; SPRINT-2, Table B-54, p118 and Poordad et al 2011<sup>5</sup>; ADVANCE, Table B-55, pp118-119; QUEST-1, Table B-50, p115 and Table B-56, pp119-120; QUEST-2, Table B-51, p115 and Table B-57, p121; ION-2, Table B-80, pp141-142; RESPOND-2, Table B-81, p143; Flamm et al 2013, Table B-77, p139; REALIZE, Table B-82, p145; PROMISE, Table B-83, p146.

- 6.10 The number of cirrhotic patients in both ION-1 (n=34) and ION-2 (n=22) were too small to accurately estimate the SVR rates in these populations. The ESC noted the numerically lower SVR among treatment experienced cirrhotic patients (19/22), and noted the FDA recommendation to treat for 24 weeks in this population, and the numerically higher SVR (74/77) observed with the addition of RBV (LDV/SOF12+R12, M. Bourliere et al., Abstract LB-6, AASLD November, 2014).
- 6.11 Comparisons of SVR rates across studies, between ledipasvir/sofosbuvir (LDV/SOF) and protease inhibitors + PR, were unadjusted indirect single arm comparisons. It was unclear to what extent the differences in observed SVR rates between the studies were a result of the different efficacies of the treatment regimens, or due to non-exchangeable populations or biases introduced into the studies. While the SVR rates for LDV/SOF were consistently higher than those for boceprevir, telaprevir or simeprevir, the magnitude of this difference was uncertain.

#### **Comparative harms**

- 6.12 LDV/SOF related adverse events of grade 3 or worse were uncommon (3.2% or less in all treatment arms except LDV/SOF24 (9.2%) and LDV/SOF+R24 (7.2%) in ION-2).
- 6.13 The pooled safety data for the treatment arms relevant to the proposed LDV/SOF PBS listing, as well as the current PBS listings of the protease inhibitors, are summarised below.

**Pooled adverse event rates for the relevant treatment arms**

	LDV/SOF	BOC+PR	TVR+PR	SMV+PR
n/N (%)	<u>ION-1</u> LDV/SOF12	<u>SPRINT-2</u> BOC+PR 24-48 RGT BOC+PR 48	<u>ADVANCE</u> T12PR 24-48 RGT	<u>QUEST-1</u> SMV+PR 24-48 RGT
	<u>ION-3</u> LDV/SOF8	<u>RESPOND-2</u> BOC+PR 36-48 RGT BOC+PR 48	<u>REALIZE</u> T12PR48	<u>QUEST-2</u> SMV+PR 24-48 RGT
	<u>ION-2</u> LDV/SOF12	<u>Flamm 2013</u> BOC+PR 48		<u>PROMISE</u> SMV+PR 48
Any AE	386/538 (71.7%)	1184/1191 (99.4%)	621/629 (98.7%)	757/781 (96.9%)
SAE	6/538 (1.1%)	144/1191 (12.1%)	66/629 (10.5%)	40/781 (5.1%)
Treatment discontinued due to AE	0/538 (0%)	161/1191 (13.5%)	75/629 (11.9%)	15/781 (1.9%)
Death <sup>a</sup>	0/538 (0%)	5/1191 (0.4%)	0/363 (0%)	2/521 (0.4%)
Anaemia	2/538 (0.4%)	572/1191 (48%)	214/629 (34%)	150/781 (19.2%)
Dysgeusia <sup>b</sup>	6/538 (1.1%)	486/1191 (40.8%)	33/266 (12.4%)	NR
Rash <sup>c</sup>	21/538 (3.9%)	79/457 (17.3%)	232/629 (36.9%)	218/781 (27.9%)
Fatigue <sup>d</sup>	112/538 (20.8%)	584/1057 (55.3%)	352/629 (56%)	178/517 (34.4%)
Headache <sup>d</sup>	110/538 (20.4%)	464/1057 (43.9%)	260/629 (41.3%)	186/517 (36%)
Nausea <sup>e</sup>	52/538 (9.7%)	468/1057 (44.3%)	250/629 (39.7%)	NR
Influenza-like illness <sup>f</sup>	6/538 (1.1%)	75/323 (23.2%)	187/629 (29.7%)	144/517 (27.9%)
Neutropenia <sup>g</sup>	NR	42/134 (31.3%)	89/629 (14.1%)	164/781 (21%)

<sup>a</sup>Death was not reported for REALIZE or PROMISE; <sup>b</sup>Dysgeusia was not reported for ADVANCE, QUEST-1, QUEST-2 or PROMISE; <sup>c</sup>Rash was not reported for SPRINT-2; <sup>d</sup>Fatigue and Headache were not reported for Flamm 2013 or QUEST-1; <sup>e</sup>Nausea was not reported for Flamm 2013, QUEST-1, QUEST-2 or PROMISE; <sup>f</sup>Influenza-like illness was not reported for SPRINT-2, Flamm 2013 and QUEST-1; <sup>g</sup>Neutropenia was not reported for ION-1, ION-2, ION-3, SPRINT-2 and RESPOND-2. Denominators represent the pooled number of patients from the studies that reported a particular adverse event.

AE= adverse event; SAE = serious adverse event; LDV/SOF = ledipasvir/sofosbuvir; BOC = boceprevir; PR = peginterferon and ribavirin; TVR = telaprevir; SMV = simeprevir; RGT = response guided therapy.

Source: generated during the evaluation - adapted from Table B-118, p178 of the submission. Only the treatment arms relevant to the submission have been included.

**Benefits/harms**

- 6.14 From the evidence in the submission, the following comparative benefits and harms of LDV/SOF, relative to 'no treatment', were estimated. When compared to protease inhibitors + PR, LDV/SOF was likely to have fewer harms (see the table above).

**The benefit/harm of LDV/SOF compared with no treatment**

Patient group	Comparison	Benefits/harms
Genotype 1, treatment naïve, non-cirrhotic patients	for every 100 patients treated with LDV/SOF for 8 weeks in comparison to <u>no treatment</u>	<ul style="list-style-type: none"> <li>Approximately 94 additional patients would be expected to achieve an SVR; and</li> <li>Approximately 1 additional patient would experience a serious adverse event.</li> </ul>
Genotype 1, treatment naïve, cirrhotic patients	for every 100 patients treated with LDV/SOF for 12 weeks in comparison to <u>no treatment</u> :	<ul style="list-style-type: none"> <li>Approximately 94 additional patients would be expected to achieve SVR; and</li> <li>Approximately 1 additional patient would experience a serious adverse event.</li> </ul>
Genotype 1, treatment experienced, non-cirrhotic patients	for every 100 patients treated with LDV/SOF for 12 weeks in comparison to <u>no treatment</u> :	<ul style="list-style-type: none"> <li>Approximately 95 additional patients would be expected to achieve an SVR, and</li> <li>Approximately 1 additional patient would experience a serious adverse event.</li> </ul>
Genotype 1, treatment experienced, cirrhotic patients	for every 100 patients treated with LDV/SOF for 12 weeks in comparison to <u>no treatment</u> :	<ul style="list-style-type: none"> <li>Approximately 86 additional patients would be expected to achieve an SVR, and</li> <li>Approximately 1 additional patient would experience a serious adverse event</li> </ul>

LDV/SOF = ledipasvir/sofosbuvir; SVR = sustained virologic response.

Source: Compiled during the evaluation

**Clinical claim**

- 6.15 The submission described LDV/SOF as:
- superior in terms of efficacy and safety to the nominated comparator of a protease inhibitor +PR; and
  - superior in terms of efficacy and with an acceptable safety profile compared with no treatment.
- 6.16 The ESC considered that the submission’s claim was reasonable, although the magnitude of differences in terms of SVR rates or rates of adverse events was uncertain due to reliance on the single arm trials, some of which involved a small number of patients.
- 6.17 Compared with no treatment, LDV/SOF was likely to be inferior in terms of safety.
- 6.18 The PBAC considered that the claim of superior comparative effectiveness and inferior comparative safety to no treatment was reasonably supported by the data in the submission for GT1 naïve and experienced cirrhotic/non-cirrhotic patients.

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

**Economic analysis**

- 6.19 The submission presented 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.

**Summary of model structure and rationale**

Time horizon	30 years. This is consistent with PBAC Advice (Para 7.10, Item 5.17 Sofosbuvir Public Summary Document, July 2014 PBAC meeting).
Outcomes	Life years gained (LYG) and quality adjusted life years (QALYs).
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. Cohort expected value analysis.
Cycle length	Three monthly cycles for the first two years, followed by yearly cycles.
Transition probabilities	Based on literature review. A number of these transition probabilities differed from those in the concurrent sofosbuvir re-submission. The LDV/SOF submission did not justify the use of these variables.
Discount rate	5% for costs and outcomes
Software package	Microsoft Excel 2013.

Source: compiled during the evaluation

- 6.20 A number of SVR rates used in the model could not be verified and differed from those reported in Section B of the submission. Most notably, for the SVR rate for treatment experienced patients who received treatment with boceprevir+PR, the SVR rate from the relevant trial (RESPOND Group 3) was 77.3%, while the SVR used in the model was 35.3%. The SVR rate for LDV/SOF observed from ION-3 was 94%, while the model used a SVR of 97.10%.
- 6.21 Transition probabilities describing the natural history of genotype 1 HCV differed between the LDV/SOF model and the model in the sofosbuvir re-submission for the same population. The submission failed to justify the use of these transition probabilities. The transition probabilities in the LDV/SOF model were consistently higher than those used in the sofosbuvir model and biased the results of the economic evaluation in favour of LDV/SOF.
- 6.22 Key drivers of the model are summarised in the table below.

**Key drivers of the model**

Description	Method/Value	Impact
Time horizon	30 years, consistent with PBAC recommendations	High, longer time horizon favours LDV/SOF
Transition probabilities particularly for: <ul style="list-style-type: none"> <li>• non-cirrhotic disease to compensated cirrhosis, and</li> <li>• compensated cirrhosis to decompensated cirrhosis and hepatocellular carcinoma.</li> </ul>	These transition probabilities were consistently higher than those used in the concurrent sofosbuvir re-submission. The use of these transition probabilities was not justified, and some could not be verified based on the source provided in the submission. See Section D.4 of the commentary (Transition Probabilities).	High, favours LDV/SOF
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 associated with 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. The utility increment associated with obtaining SVR in the LDV/SOF model (0.041) was more conservative than in the sofosbuvir re-submission (0.05).	Moderate, favours LDV/SOF

Source: compiled during the evaluation

6.23 The economic model provided by the submission contained the following referencing errors:

- The outcomes for treatment naïve non-cirrhotic patients incorrectly referenced the treatment naïve compensated cirrhosis Markov trace.
- The outcomes for treatment naïve compensated cirrhosis patients incorrectly referenced the treatment experienced non-cirrhotic Markov trace.
- The Markov trace for treatment-experienced non-cirrhotic referenced the SVR rate for treatment-naïve patients with compensated cirrhosis.

These referencing errors were corrected during the evaluation.

6.24 The submission assumed that the duration of treatment with LDV/SOF for treatment naïve non-cirrhotic patients was 10 weeks. During the evaluation, this was adjusted to 8 weeks, consistent with the proposed PBS listing. In addition, the SVR rates that were reported in the clinical studies in Section B were incorporated in the updated model during the evaluation. The adjusted results of the economic evaluation are summarised below. Results were presented against the comparators of simeprevir, sofosbuvir and no treatment for treatment-naïve patients and simeprevir and no treatment for treatment-experienced patients. The ESC noted the sponsor's correction of the referencing errors, SVR rates, and treatment duration (from 10 to 8 weeks) in the PSCR. One referencing error was not identified and the detail of the error was presented in the ESC Advice for this item.

**Results of the economic evaluation of LDV/SOF compared with no treatment, SOF+PR and SMV+PR using transition probabilities from the submission**

Treatment-naïve			
	Comparator		
	No Treatment	SOF+PR	SMV+PR
Incremental cost	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Incremental QALYs	1.4999	0.1349	0.3670
ICER	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Treatment-experienced			
	Comparator		
	No treatment	SMV+PR	
Incremental cost	\$ [REDACTED]	\$ [REDACTED]	
Incremental QALYs	1.4802	0.3496	
ICER	\$ [REDACTED]	\$ [REDACTED]	

LDV/SOF = ledipasvir/sofosbuvir; SOF = sofosbuvir; PR = peginterferon and ribavirin; SMV = simeprevir; QALY = quality-adjusted life year; ICER = incremental cost effectiveness ratio

Proportion of patients entering the model with cirrhosis assumed to be 14%.

Source: Compiled during the evaluation

- During the evaluation, the incremental cost-effectiveness of LDV/SOF in comparison with no treatment was re-calculated with the transition probabilities used in the sofosbuvir resubmission. The ICERs for different subgroups are presented in the table below, adjusting the following transition probabilities:
  - non-cirrhotic to compensated cirrhosis (0.016 to 0.010);
  - Compensated cirrhosis to decompensated cirrhosis (0.0438 to 0.039);
  - compensated cirrhosis to hepatocellular carcinoma (0.0631 to 0.014).
- The ESC noted that transition probabilities chosen in the submission were less conservative than those used in the SOF resubmission. The ESC also noted the sponsor's response in the PSCR that the proposed transition probabilities may better reflect transition probabilities for an older treatment cohort. The ESC disagreed with this interpretation as both models (LDV/SOF and SOF) applied 47 years as the average age of treatment. The ESC considered that the same transition probabilities should be used in both the LDV/SOF model and the SOF model. The ESC considered that it was appropriate to use the more conservative values used in the SOF model to inform the base case analysis. The ESC noted, using the corrected transition probabilities, for treatment-naïve patients against no treatment, the ICER increased from \$15,000/QALY - \$45,000/QALY to \$15,000/QALY - \$45,000/QALY (non-cirrhotic) and \$15,000/QALY - \$45,000/QALY to \$15,000/QALY - \$45,000/QALY (cirrhotic).

**Adjusted results for using transition probabilities from this submission and the sofosbuvir resubmission**

Comparator	ICER			
	TNNC	TNCC	TENC	TECC
<b>Using transition probabilities (LDV/SOF model)</b>				
No Treatment	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
SOF+PEG+RBV	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
SMV+PEG+RBV	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
<b>Using transition probabilities (SOF model)</b>				
No Treatment	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
SOF+PEG+RBV	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
SMV+PEG+RBV	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]

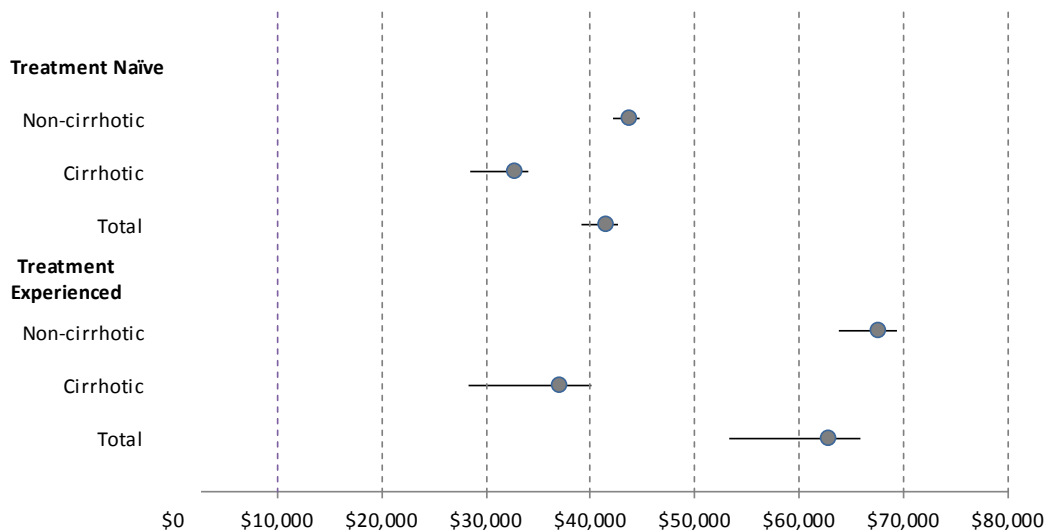
TNNC=treatment-naïve non-cirrhotic; TNCC=treatment-naïve compensated cirrhosis; TENC=treatment-experienced non-cirrhotic; TECC=treatment-experienced compensated cirrhosis; TN=treatment-naïve; TE=treatment-experienced

^Proposed PBS listing for SOF does not include treatment experienced genotype 1 patients

Source: Table D.6.1 of the Commentary

6.25 Sensitivity analyses were performed using the 95% confidence interval of SVR rates observed from the respective studies and the transmission probabilities in the SOF resubmission. Results are presented in the figure below. The ESC noted that the upper 95%CI for the ICERs was highest for non-cirrhotic treatment experienced patients

Results of the sensitivity analyses: Using the lower and upper 95% confidence intervals for SVR Rates, LDV/SOF vs No Treatment, using transition probabilities from the SOF resubmission



Total weighted by 14% cirrhotic patients and 86% non-cirrhotic patients

Source: Figure.D.6.4 of the commentary.

- 6.26 The Food and Drug Administration (FDA) have recommended LDV/SOF regimens that differ to the proposed PBS listing:
- Treatment-naïve non-cirrhotic patients: LDV/SOF 12 weeks, compared to LDV/SOF 8 weeks in the proposed listing; and
  - Treatment-experienced cirrhotic patients: LDV/SOF 24 weeks, compared to LDV/SOF 12 weeks in the proposed listing.
  - During the evaluation, a sensitivity analysis was conducted using the proposed treatment regimen and the FDA recommended treatment regimen for these two subpopulations. For example, if 100% of treatment-naïve non-cirrhotic patients were treated with LDV/SOF for 12 weeks applying the transition probabilities from the SOF resubmission, the ICER was \$45,000/QALY - \$75,000/QALY. The ESC considered that there is the potential for many treatment naïve high-grade fibrosis patients to be treated like cirrhosis patients, that is, with LDV12/SOF12 instead of LDV8/SOF8 (in line with United States guidelines). In that case the ICER will have been underestimated.
- 6.27 The ESC noted that the PSCR contained typographical errors:
- The transition probability for compensated cirrhosis to decompensated cirrhosis was incorrectly identified as 0.04075 for the LDV/SOF model and 0.0438 in the SOF model. The LDV/SOF model has used 0.0438 (Cardoso et al, 2010), while the SOF model has used 0.039 (Fattovitch, 1997).
  - The transition probability from compensated cirrhosis to hepatocellular carcinoma was incorrectly identified as 0.016 in the LDV/SOF model and 0.010 in the SOF model. The LDV/SOF model uses 0.0631 (Cardoso, et al, 2010) while the SOF model uses 0.014 (Fattovitch, 1997).
- 6.28 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) showed that 45-60% of patients treated with interferon-free regimens were cirrhotic. ([http://www.natap.org/2014/AASLDEASL/AASLDEASL\\_01.htm](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.
- 6.29 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. .
- 6.30 The PBAC accepted the revised base case presented in the ESC. The PBAC agreed with ESC that the economic models to inform the analysis of SOF and LDV/SOF should use the same transition probabilities.

- 6.31 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 - \$45,000. 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 a 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.
- 6.32 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 re-submission. The PBAC noted that there were some differences in assumptions and inputs between the models in the SOF re-submission and LDV/SOF submission. Overall, the PBAC preferred valuing the cost-effectiveness of SOF-containing treatments using the model provided in the SOF resubmission. 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 at a \$15,000/QALY, the cost of LDV/SOF for 8 weeks in the revised base case LDV/SOF model was lower than derived from the SOF model.
- 6.33 The PBAC noted in the pre-PBAC response that treatment durations in the Product information might be different to those proposed in the submission. The PBAC recommended that the cost to achieve a SVR12 should be independent of the treatment duration (such as LDV/SOF 8 weeks, 12 week or 24 weeks) considered to be appropriate to achieve a SVR in patients

**Drug cost/patient/course**

- 6.34 LDV/SOF 8 Week regimen (treatment-naïve non-cirrhotic): \$ [REDACTED]
- 6.35 LDV/SOF 12 week regimen (treatment-naïve cirrhotic and treatment experienced patients): \$ [REDACTED]

**Estimated PBS usage & financial implications**

- 6.36 The submission was considered by the Drug Utilisation Sub-Committee (DUSC).
- 6.37 The following estimates of PBS usage and financial implications were presented in the submission. At year 5, the estimated number of patients was less than 10,000 and the net cost to the PBS would be more than \$100 million.

**Estimated number of patients treated / year with ledipasvir/sofosbuvir**

Population	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Treated with ledipasvir/Sofosbuvir</b>					
Treatment naïve					
Cirrhotic	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Non Cirrhotic	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Treatment experienced					
Cirrhotic	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Non Cirrhotic	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<b>Total</b>	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Source: compiled during the evaluation from attachment 'Section E workbook – LDVSOF\_Final.xlsm'.

**Estimated net cost to the PBS/RPBS**

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>HCV genotype 1 treated population</b>					
With LDV/SOF	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Without LDV/SOF	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<b>Cost implications of PBS listing of LDV/SOF</b>					
Cost of ledipasvir/sofosbuvir	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Savings due to reduced use of superseded treatment	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
<b>Total net cost</b>	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
PBS component	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
RPBS component	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Commentary on the Main Submission, Table E.4.1 p87.

- 6.38 The DUSC considered that the estimates presented in the submission to be underestimated. The submission assumed a maximum treatment capacity of less than 10,000 patients with genotype 1 per year, which is projected to be reached by Year 3 of listing and capped at this level over the remaining forward estimates period.

DUSC considered that the uptake of ledipasvir with sofosbuvir would be expected to be higher, noting that the capacity of the health system to treat any HCV genotype through specialist liver centres with interferon-free regimens was estimated to be up to 15,000 at the February 2014 HCV Stakeholder Meeting.

- 6.39 The DUSC considered that using Gidding et al. (2012) to estimate the proportion of treated patients who are genotype 1 potentially underestimates the size of this population compared to a more recent estimate from Bruggmann et al. (2014), (49.6% vs. 54.5%, respectively).
- 6.40 The DUSC considered the financial estimates are sensitive to the assumption for cirrhotic patients who receive LDV+SOF as this patient group requires an additional 4 weeks of treatment with an associated higher regimen cost. Should LDV+SOF be prioritised initially on the basis of clinical need to cirrhotic patients, this may increase the net cost of LDV + SOF during the initial years of listing.
- 6.41 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

- 6.42 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 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 years, it is estimated that approximately 61 500 patients would be treated, and the net cost would be more than \$100 million. 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.

### Financial Management – Special Pricing and Risk Sharing Arrangements

- 6.43 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).

- 6.44 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 ledipasvir/Sofosbuvir for the treatment of Genotype 1 chronic hepatitis C (CHC) on the basis of cost-effectiveness of the treatment over no treatment.
- 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 if 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. The conditions of the listing would also depend on the final registered Product Information.
- 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 was of 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 considered that the claim of superior comparative effectiveness and inferior comparative safety to no treatment was reasonably support by the data in the submission
- 7.7 The PBAC accepted the structure of the economic model presented in the submission but considered that the base case should be respecified to that suggested by the ESC.
- 7.8 The PBAC noted the DUSC advice on the item. The PBAC accepted the estimates of patient numbers. Based on the cost per treatment in the acceptable range of cost-effectiveness: 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. 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, of the all oral treatments, as a single-sponsor combination treatment ledipasvir/sofosbuvir is likely to be the first treatment to be negotiated for listing on the PBS.
- 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, ledipasvir/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 ledipasvir/sofosbuvir by nurse practitioners would depend on the final listing conditions of ledipasvir/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 resubmission is not eligible for an Independent Review, because the PBAC made a positive recommendation
- 7.14 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.

7.15 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 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.