6.03 SIMEPREVIR capsule, 150mg, OLYSIO®; Janssen-Cilag Pty Ltd.

1 Purpose of Application

1.1 The submission requested a Section 100 (Highly Specialised Drugs Program) Authority Required (Streamlined) listing for simeprevir in combination with sofosbuvir (SMV+SOF) for the treatment of patients with genotype 1 chronic hepatitis C (CHC) infection who have compensated liver disease, irrespective of previous treatment history.

2 Requested listing

2.1 The requested listings, including proposed changes in Pre-Sub-Committee-Response (PSCR) are:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
SIMEPREVIR Capsule 150mg, 7	4	2	$[redacted] (Public) $[redacted] (Private)	OLYSIO® Janssen-Cilag Pty Ltd

General Schedule	
Treatment phase: Patients who have not received prior treatment for CHC (treatment-naïve)	
Condition	Chronic genotype 1 hepatitis C infection
Restriction	Authority Required
Treatment criteria	• Must be treated in an accredited treatment centre • Evidence of chronic genotype 1 hepatitis C infection (repeatedly ant-HCV positive and HCV RNA positive) must be documented in the patient's medical records
Clinical criteria	• Patient must have compensated liver disease, • Patient must have not received prior treatment for chronic hepatitis C, • The treatment must be in combination with sofosbuvir, • The treatment with simeprevir must be limited to a maximum duration of 12 weeks.
Population criteria	Patient must be 18 year or older
Notes	• No increase in the maximum quantity or number of units may be authorised • No increase in the maximum number of repeats may be authorised • Treatment centres are required to have access to the following appropriate specialist facilities for the provision of clinical 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.
Treatment phase: Patients who have received prior treatment for CHC (treatment-experienced)	
Condition	Chronic genotype 1 hepatitis C infection
Restriction	Authority Required
Treatment criteria	• Must be treated in an accredited treatment centre • Evidence of chronic genotype 1 hepatitis C infection (repeatedly ant-HCV positive and HCV RNA positive) must be documented in the patient's medical records
Clinical criteria	• Patient must have compensated liver disease, • Patient must have received prior treatment for chronic hepatitis C, • The treatment must be in combination with sofosbuvir,

	• The treatment with simeprevir must be limited to a maximum duration of 12 weeks.
Population criteria	Patient must be 18 year or older
Notes	• No increase in the maximum quantity or number of units may be authorised • No increase in the maximum number of repeats may be authorised • Treatment centres are required to have access to the following appropriate specialist facilities for the provision of clinical 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.

CHC = chronic hepatitis C; HCV = hepatitis C virus; RNA = ribonucleic acid.

2.2 The ESC noted the sponsor's revised request in the PSCR for the maximum quantity of SMV to be amended from six to four packs, and from one repeat to two repeats, providing a total of 12 weeks of SIM+SOF therapy, compared to the current listing of maximum quantity of 6 and zero repeats.

2.3 The requested listing for patients who had received prior treatments did not restrict the eligibility for 12 weeks of SMV+SOF treatment according to the type of prior therapies received. Specifically, the requested listing did not preclude re-treatment of patients who had previously failed simeprevir in combination with peginterferon and ribavirin (SMV+PR), or an alternative sofosbuvir-based regimen, or other interferon-free regimens involving direct acting antivirals (DAAs). There was no clinical evidence provided to support the listing of SMV+SOF in patients who had previously been treated with regimens other than PR (i.e. DAA-based regimens).

2.4 The PSCR and pre-PBAC response provided information of studies including patients who have failed prior protease inhibitor + PR, daclatasvir + PR or asunaprevir + daclatasvir + PR therapy.

2.5 The ESC noted that cirrhotic patients previously treated with protease inhibitors may not respond as well to SMV+SOF compared to treatment naïve patients, or compared to protease inhibitor experienced cirrhotic patients treated with DAA-only combinations which do not contain a protease inhibitor, because of the potential emergence of mutations conferring resistance to protease inhibitors.

2.6 The requested restriction did not preclude concomitant administration of ribavirin. There were insufficient data to determine whether the addition of ribavirin to SMV+SOF, given over 12 weeks (SMV12+SOF12), would provide any additional benefit in difficult-to-treat subgroups such as treatment-experienced patients with cirrhosis. However, the results of the COSMOS study suggest that the addition of ribavirin to SMV12+SOF12 is associated with an increase in adverse effects. The PSCR (p1) stated that the sponsor was willing to amend the restriction to exclude use with ribavirin.

2.7 Both the Food and Drug Administration (FDA) prescribing information for simeprevir and the current American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) guidelines for hepatitis C recommend 24 weeks of SMV+SOF in patients with cirrhosis[1, 2]. The AASLD/IDSA guidelines also indicate that the addition of ribavirin to the treatment regimen could be considered in some patient subgroups.

2.8 At its March 2015 meeting, the PBAC recommended a General Schedule listing of other treatments for CHC. In this submission, the sponsor requested a Section 100 (Highly Specialised Drugs Program) Authority Required (Streamlined) listing for simeprevir in combination with sofosbuvir. The ESC noted the sponsor's revised request in the PSCR for a Section 85 listing in line with the PBAC March 2015 recommendations for other DAA therapies.

2.9 The requested listing did not preclude treatment for patients who have co-infection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV). There was no clinical evidence for the effectiveness and safety of SMV+SOF in patients with these co-infections. The PSCR (p4) provided information on the treatment of patients co-infected with HBV or HIV. The ESC noted that the current listings for CHC do not specifically exclude use in co-infected patients.

2.10 Listing was sought on the basis that SMV12+SOF12 was cost-effective relative to a mixed comparator of active treatment (a protease inhibitor (PI) in combination with PR) and no treatment.

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

3 Background

3.1 The submission was made under the TGA/PBAC Parallel Process. Simeprevir was listed on the Australian Register of Therapeutic Goods on the 17th July 2014 for the following indication:

> For the treatment of chronic hepatitis C (CHC) genotype 1 or genotype 4 infection, in combination with other medicinal products for the treatment of CHC infection.

3.2 The Dosage and Administration section of the current TGA-approved Product Information of simeprevir stipulates that it must be administered in combination with PR.

3.3 According to the submission, an application had been lodged with the TGA to request changes to the Dosage and Administration section of the current Product Information. These changes related to recommendations on the use of simeprevir in combination with sofosbuvir. The current timelines indicate that the TGA clinical evaluation report is expected to be available by the end of August 2015. The TGA delegate's overview is scheduled to be received by 3 November 2015.

3.4 Simeprevir was recommended for Section 100 (Highly Specialised Drugs Program) listing on the PBS for treatment of chronic genotype 1 hepatitis C infection in combination with PR at the July 2014 PBAC meeting.

3.5 Sofosbuvir was recommended for Section 85 Authority Required listing at the March 2015 PBAC meeting for the treatment of CHC.

3.6 This is the first submission to the PBAC for simeprevir in combination with sofosbuvir for the treatment of genotype 1 CHC.

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

4 Clinical place for the proposed therapy

4.1 Hepatitis C virus (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 CHC accounts for 49-55% of infections in Australia.

4.2 Boceprevir, telaprevir and simeprevir (three HCV NS3/4A inhibitors) are currently reimbursed on the PBS for the treatment of HCV Genotype 1 in combination with PR.

4.3 Sofosbuvir, ledipasvir/sofosbuvir fixed dose combination (LDV/SOF), and daclatasvir in combination with sofosbuvir (DCV+SOF) were recommended at the March 2015 PBAC meeting for the treatment of genotype 1 CHC.

4.4 Both simeprevir and sofosbuvir are DAAs. Simeprevir is an inhibitor of hepatitis C virus NS3/4A protease which is essential for viral replication. Sofosbuvir is a nucleotide inhibitor of HCV NS5B ribonucleic acid (RNA) polymerase, which is also essential for viral replication. By targeting different proteins in the HCV life cycle, simeprevir and sofosbuvir complement each other in the treatment of patients with genotype 1 HCV patients and compensated liver disease.

4.5 The proposed dose regimen for both treatment-naïve and treatment-experienced patients with genotype 1 HCV infection, with or without cirrhosis, is simeprevir 150mg once daily with food, in combination with sofosbuvir 400mg once daily, for 12 weeks.

4.6 The ESC noted that in trials previously considered by the PBAC among treatment naïve genotype 1 patients, the range of observed SVR following treatment with boceprevir (BOC), telaprevir (TVR) or simeprevir (SMV) in combination with PR was 62.6% to 80.5%, while the observed SVR observed for PR alone ranged from 36.4% to 65.9%.

Table 1: observed SVR following treatment with boceprevir (BOC), telaprevir (TVR) or simeprevir (SMV) and peginterferon and ribavirin (PR)

Regimen	Trial ID	n/N (%)
SMV12 weeks+PR24/48 weeks	QUEST 1 SVR (12)	210/264 (79.5%)
	QUEST 2 SVR (12)	207/257 (80.5%)
	PILLAR SVR (24)	62/77 (80.5%)
TVR12 weeks +PR24/48 weeks	ADVANCE SVR (24)	271/363 (74.7%)]
BOC24+PR28/48 weeks	SPRINT 2 SVR (24)	230/368 (62.6%)
PR 48 weeks	QUEST 1 SVR (12)	64/130 (49.2%)
	QUEST 2 SVR (12)	67/134 (50.0%)
	PILLAR SVR (24)	50/77 (64.9%)
	ADVANCE SVR (24)	158/361 (43.8%)
	SPRINT 2 SVR (24)	132/363 (36.4%)

5 Comparator

5.1 The submission nominated the following as the main comparators:

- SMV+PR - for those patients with genotype 1 HCV who are currently receiving interferon-containing treatment regimens; and
- No treatment - for eligible patients who are currently not being treated.

5.2 As many patients have not been receiving active treatment while awaiting the emergence of interferon-free treatment regimens (5.17 Sofosbuvir Public Summary Document, paragraph 7.5, July 2014 PBAC meeting), the PBAC have previously accepted the appropriate comparator for the majority of patients was 'no treatment'. The ESC reiterated that this is the appropriate comparator in the scenario of awaiting the availability of IFN-free treatments.

5.3 Recognising that the PBAC had recently considered other interferon-free regimens for the treatment of genotype 1 HCV, the submission nominated the following supplementary comparators:

- Ledipasvir/sofosbuvir fixed dose combination (LDV/SOF)
- Daclatasvir + sofosbuvir (DCV+SOF)
- Daclatasvir + asunaprevir (DCV+ASV) (for genotype 1b), and
- Paritaprevir/ritonavir/ombitasvir + dasabuvir ± ribavirin (Viekira PAK/Viekira PAK-RBV)

5.4 Both LDV/SOF and DCV+SOF were recommended for listing for treatment of chronic genotype 1 HCV infection at the March 2015 PBAC meeting. It is likely that the interferon-free regimens will become the standard of care and can be considered an appropriate comparator. The comparison with Viekira PAK/Viekira PAK-RBV (considered at the same meeting) was also presented. Asunaprevir was rejected for PBS listing at the March 2015 PBAC meeting and so comparisons with this drug were not considered in the evaluation.

5.5 Therefore, the evaluation focused on the comparison with 'no treatment' and interferon-free treatments in the clinical assessment.

5.6 The ESC noted the sponsor's request in the PSCR for SIM+SOF to be considered non-inferior to LDV/SOF, DAC+SOF and Viekira PAK +/- RBV. The PBAC considered that the IFN-free treatments presented in the submission were appropriate comparators, particularly as availability of the SIM + SOF regimen, required listing of SOF.

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 (78), health care professionals (16) and organisations (17) via the Consumer Comments facility on the PBS website. The large number of comments and discussion reiterate the comments received during previous considerations of the IFN-free treatments, namely 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.

6.3 The PBAC recalled the discussion during meeting of the representatives of the PBAC with Hepatitis Australia, Hepatitis NSW, the Australian Injecting and the Illicit Drug User's League prior to the March 2015 PBAC meeting.

6.4 The PBAC noted and welcomed this input.

Clinical trials

6.5 The submission was based on:

- A randomised trial comparing SMV12+SOF12 to SMV8+SOF8 in both treatment-naïve and treatment-experienced patients with genotype 1 HCV infection without cirrhosis (Study 3017);
- A single-arm study assessing SMV12+SOF12 in treatment-naïve and treatment-experienced patients with genotype 1 HCV infection with cirrhosis (Study 3018);
- A head-to-head randomised trial comparing SMV12+SOF12 with SOF12+PR12 in both treatment-naïve and treatment-experienced patients with chronic HCV genotype 1a infection and cirrhosis (Pearlman 2015); and
- A single treatment arm from an open-label randomised trial comparing four different regimens of SMV+SOF with or without ribavirin (RBV) in treatment-naïve and treatment-experienced patients with chronic HCV genotype 1 infection (COSMOS).

6.6 The comparative effectiveness of the alternative interferon-free regimens was estimated in the submission through the use of unadjusted indirect comparisons of single treatment arms from the following studies:

- LDV/SOF: ION-1, ION-2, ION-3;
- DCV+SOF: Study 4040 in non-cirrhotic HCV patients;
- Viekira PAK/Viekira PAK-RBV: Pearl II, Pearl III, Pearl IV, Turquoise II, Sapphire I and Sapphire II.

6.7 Details of the trials presented in the submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Simeprevir + sofosbuvir		
Direct randomised trial of SMV+SOF compared to SOF+PR		
Pearlman 2015	Pearlman B, Ehleben C, et al. The combination of simeprevir and sofosbuvir is more effective than that of peginterferon, ribavirin, and sofosbuvir for patients with hepatitis C-related Child's class A cirrhosis.	Gastroenterology 2015; 148 (4):762-770.
Single arms from randomised trials		
Study 3017	Clinical Protocol Study 3017 Study 3017 Topline Results, Interim Analysis: SVR12. A Phase 3, multicentre, randomised, open-label study to investigate the efficacy and safety of a 12- or 8- week treatment regimen of simeprevir in combination with sofosbuvir in treatment-naïve and experienced subjects with chronic genotype 1 hepatitis C virus infection without cirrhosis.	[redacted]
COSMOS	Clinical Study Report 2002: An exploratory Phase IIa, randomised, open-label trial to investigate the efficacy and safety of 12 weeks or 24 weeks of TMC435 in combination with PSI-7977 with or without ribavirin in chronic	[redacted]

	hepatitis C genotype 1-infected prior null responders to peginterferon/ribavirin therapy or HCV treatment-naïve subjects	
	Lawitz E., Sulkowski M.S., et al. (2014). Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naïve patients: the COSMOS randomised study.	The Lancet 2014; 384 (9956):1756-1765.
Non-comparative studies		
Study 3018	Clinical Protocol Study 3018. Study 3018 Topline Results, Interim analysis: SVR12. A phase 3, multicentre, open-label, single-arm study to investigate the efficacy and safety of a 12-Week regimen of simeprevir in combination with sofosbuvir in treatment-naïve or -experienced subjects with chronic genotype 1 hepatitis C virus infection and cirrhosis.	[redacted]
Ledipasvir/sofosbuvir		
Single arms from randomised trials		
ION-1	Afdhal N, Zeuzem S, et al. (2014). Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection.	New England Journal of Medicine 2014; 370 (20):1889-1898.
ION-2	Afdhal N, Reddy K.R., et al. (2014). Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection.	New England Journal of Medicine 2014; 370 (16):1483-1493.
ION-3	Kowdley K.V., Gordon S.C., et al. (2014). Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis.	New England Journal of Medicine 2014; 370 (20):1879-1888.
Daclatasvir		
Single arms from randomised trials		
HALLMARK-DUAL	Manns M, Pol S., et al. (2014). All-oral daclatasvir plus asunaprevir for hepatitis C virus genotype 1b: a multinational, phase 3, multicohort study.	The Lancet 2014; 384:1597-1605.
Study 4040	Sulkowski M.S., Gardiner D.F., et al. (2014). Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection.	New England Journal of Medicine 2014; 370 (3):211-221.
Paritaprevir/ritonavir/ombitasvir + dasabuvir ± ribavirin		
Single arms from randomised trials		
PEARL II	Andreone P., Colombo, M.G., et al (2014). ABT450, Ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment experienced patients with HCV genotype 1b infection.	Gastroenterology (2014); 147:359-365.
PEARL III and PEARL IV	Ferenci P.F., Bernstein D., et al (2014). ABT450/r–Ombitasvir and Dasabuvir with or without Ribavirin for HCV.	New England Journal of Medicine (2014); 370 (21):1983-1992.
TURQUOISE II	Poordad F., Hezode C. et al. (2014). ABT450/r–ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis.	New England Journal of Medicine (2014); 370 (21):1973-1982.
SAPPHIRE I	Feld J.J., Kowdley K.V. et al (2014). Treatment	New England Journal of Medicine (2014); 370

	of HCV with ABT450/r–ombitasvir and dasabuvir with ribavirin.	(17):1594-1603.
SAPPHIRE II	Zeuzem S., Jacolson I.M., et al (2014). Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin.	New England Journal of Medicine (2014); 370 (17): 1604-1614.

Source: Table Bi.7, pp35-36 Section Bi of the submission; Table Bii.2.4, p101 Section Bii of the submission

6.8 The key features of the included evidence are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias[a]	Patient population	Outcome	Use in modelled evaluation
SMF+SOF						
Study 3017	155	Single arm of R, OL 24 weeks post treatment	High/unclear	GT1 non-cirrhotic	SVR12	Used*
Study 3018	103	Single arm, OL 24 weeks post treatment	High/unclear	GT1 cirrhotic	SVR12	Used*
Pearlman 2015	58[b]	Single arm of R, OL 12 weeks post treatment	High/unclear	GT1a cirrhotic patients	SVR12	Not used
COSMOS	28	Single arm of R, OL 36 weeks post treatment	High/unclear	GT1 both cirrhotic and non-cirrhotic	SVR12	Used**
Daclatasvir						
Study 4040	62	Two arms of R, OL 24 weeks post treatment	High/unclear	GT1 non-cirrhotic	SVR12	N/A
LDV/SOF						
ION-1 LDV/SOF 12 weeks	34	Single arm of R, OL 12 weeks post treatment	High/low	Treatment-naïve cirrhotic	SVR12	N/A
ION-3 LDV/SOF 8/12 weeks	431	Single arm of R, OL 12 weeks post treatment	High/low	Treatment-naïve, non-cirrhotic	SVR12	N/A
ION-2 LDV/SOF 12 weeks	109	Single arm of R, OL 12 weeks post treatment	High/low	Treatment-experienced (both non-cirrhotic and cirrhotic)	SVR12	N/A
Viekira PAK/Viekira PAK-RBV						
Turquoise II	380[c]	Single arm of R, OL 48 weeks	High/low	Treatment-naïve and experienced cirrhotic	SVR12	N/A
Pearl II	95	Single arm of R, OL 48 weeks	High/low	GT1b treatment-experienced	SVR12	N/A
Pearl III	209	R, DB 48 weeks	High/low	GT1b treatment-naïve non-cirrhotic	SVR12	N/A
Pearl IV	100	R, DB 48 weeks	High/low	GT1a treatment-naïve non-cirrhotic	SVR12	N/A
Sapphire I	473	R, DB 48 weeks	High/low	Treatment-naïve non-cirrhotic	SVR12	N/A

Sapphire II	297	R, DB 48 weeks	High/low	Treatment-experienced non-cirrhotic	SVR12	N/A

*Used during the evaluation
**Used in the submission
DB=double blind; R = randomised; OL=open label; SVR = sustained virologic response; N/A = not applicable.
[a] Refers to bias associated with indirect comparison between SMV+SOF and each interferon-free regimen and between each interferon-free regimen and no treatment.
[b] 62 patients were randomised to SMV12+SOF12. Four of them (6.5%) could not get third-party payer approval for their medication and were withdrawn from the trial.
[c] 208 patients were assigned to a 12 week regimen and 172 patients to a 24 week regimen.
Source: compiled during the evaluation

Comparative effectiveness

6.9 The table below summarises the results for the primary outcome, sustained virologic response 12 weeks after end of treatment (SVR12), for the SMV12+SOF12 treatment arm in each included study.

Table 4: Results of SVR12 in the SMV12+SOF12 treatment arm across the studies

Patient subgroup	Study 3017[b] n/N (%) [95% CI]	Study 3018[c,d] n/N (%) [95% CI]	Pearlman 2015[a] n/N (%) [95% CI]	COSMOS n/N (%) [95% CI]
Treatment-naïve	112/115 (97.4%) [%, %]	44/50 (88.0%) [%, %]	21/22 (95.5%) [%, %]	6/7 (85.7%) [%, %]
Non-cirrhotic	112/115 (97.4%)	-	-	4/4 (100%)
Cirrhotic	-	44/50 (88.0%)	21/22 (95.5%)	2/3 (66.7%)
Treatment-experienced	38/40 (95.0%) [%, %]	42/53 (79.2%) [%, %]	33/36 (91.7%) [%, %]	20/21 (95.2%) [%, %]
Non-cirrhotic	38/40 (95.0%)	-	-	16/17 (94.1%)
Cirrhotic	-	42/53 (79.2%)	33/36 (91.7%)	4/4 (100%)
Total	**150/155 (96.8%) [%, %]**	**86/103 (83.5%) [%, %]**	**54/58 (93.1%) [%, %]**	**26/28 (92.9%) [%, %]**
Non-cirrhotic	150/155 (96.8%) [%, %]	-	-	20/21 (95.2%) [%, %]
Cirrhotic	-	86/103 (83.5%) [%, %]	54/58 (93.1%) [%, %]	6/7 (85.7%) [%, %]

CI = confidence interval; SMV = simeprevir; SOF = sofosbuvir; SVR = sustained virologic response
[a] Only includes genotype 1a patients with cirrhosis
[b] Source: Table 12, p24 of Study 3017 Topline Results Only includes non-cirrhotic patients
[c] Source: Table 11, p21 of Study 3018 Topline Results. Only includes patients with cirrhosis
[d] The SVR12 rate in the SMV8+SOF8 treatment arm was 128/155 (82.6%)
95% CI were calculated during the evaluation. Binomial exact 95%CIs calculated in STATA.
Source: Table Bi.24 and Bi.25, p73 Section Bi of the submission; Pearlman 2015; Lawitz et al 2014 (including supplementary appendix)[3]

6.10 The results from the four studies suggest that SMV12+SOF12 is effective across all genotype 1 HCV patient subgroups, with SVR12 rates ranging from 83.5% (95%CI: %, %) in Study 3018 to 96.8% (95%CI: %, %) in Study 3017.

6.11 A comparison of the SVR12 rates across Studies 3017 and 3018 suggests that SMV12+SOF12 is less effective in cirrhotic patients than in non-cirrhotic patients,

with a 13% difference between the point estimates of the SVR12 rate in the two populations.

6.12 The SVR12 rate in Pearlman 2015 was higher than that in Study 3018, although 95% confidence intervals overlapped. The Pearlman 2015 study included a higher proportion of patients with baseline characteristics traditionally associated with poor response to interferon-based therapy. The ESC noted in the PSCR (p33) the relatively high frequency of Q80K mutation in the Study 3018 population ([redacted]%), and the lower point estimate of SVR among Q80K polymorphism patients versus non-Q80K polymorphism patients in that study (74% versus 92%). The ESC noted that the current prevalence of Q80K in the Australian population is lower, as noted below.

6.13 In Study 3018, subgroup analyses reported in the Study 3018 Topline Results, indicated that, in cirrhotic genotype 1a HCV patients, the SVR12 rate was lower in patients with a baseline NS3 Q80K polymorphism (25/34, 73.5%) compared to those without (35/38, 92.1%). This difference was not evident in non-cirrhotic patients in Study 3017 (95.7% vs 97.1% in those with and without Q80K polymorphism, respectively). The ESC has previously noted that Q80K polymorphism appears to be an effect modifier for SMV+PR. Given the low prevalence of the polymorphism in Australia (approximately 5-7%), the PBAC agreed with ESC and considered that screening for Q80K polymorphism would not be necessary, provided the proportion of patients with the Q80K polymorphism does not increase significantly over time

6.14 The majority of patients with virological failure with sequencing data available had emerging NS3 mutations at the time of failure, most of which have been shown to reduce simeprevir anti-HCV activity in vitro. No emerging NS5B mutations associated with sofosbuvir were detected in these patients. The European Medicines Agency (EMA) concluded that the long-term clinical impact of the emergence or persistence of simeprevir-resistance-associated substitutions is unknown.

6.15 The results of the unadjusted indirect comparison of SMV12+SOF12 (based on the results from Study 3017 and Study 3018) and the alternative interferon-free treatment regimens for genotype 1 HCV, for the primary outcome SVR12, performed during the evaluation, are presented in the figure below.

6.16 Given the potential exchangeability issues between studies and the small sample sizes in some patient subgroups, the results of the unadjusted indirect comparisons were uncertain and must be interpreted with caution. The SVR12 rates in both treatment-naïve and treatment-experienced patients without cirrhosis were consistently high and reasonably similar across the alternative interferon-free treatment regimens. The confidence intervals of the SVR12 rates in cirrhotic patients were generally wider than those in non-cirrhotic patients, adding further uncertainty to the comparison between treatment regimens in these patients. The results from Study 3018 suggested that SMV12+SOF12 may be inferior to Viekira PAK-RBV in treatment experienced patients with cirrhosis. Conversely, the high SVR12 rate observed in Pearlman 2015 for this patient subgroup (33/36, 91.7%) was similar to the other interferon-free treatment regimens.

Figure 1: Comparison of SVR12 rates for alternative interferon-free treatment regimens for genotype 1 HCV

[THIS FIGURE HAS BEEN REDACTED]

Comparative harms

6.17 The proportion of patients experiencing adverse events (AEs) in the SMV12+SOF12 treatment arms of the included studies is summarised below. Skin events, including rash, photosensitivity and pruritus are recognised safety issues associated with simeprevir; most of these events were of mild to moderate severity.

Table 5: Summary of key adverse events in the SMV12+SOF12 treatment arm of the studies

	Study 3017[a,b] n/N (%)	Study 3018[c] n/N (%)	Pearlman 2015[d] n/N (%)	COSMOS n/N (%)
Any AE	103/155 (66.5%)	72/103 (69.9%)	46/58 (79.3%)	20/28 (71.4%)
AE related to treatment	[redacted]	50/103 (48.5%)	NR	13/28 (46.4%)
Any serious AE	1/155 (0.6%)	5/103 (4.9%)	0	0
Grade 3/4 AE	4/155 (2.6%)	6/103 (5.8%)	1/58 (1.7%)	2/28 (7.1%)
Number discontinued	0	3/103 (2.9%)	0	0
Number died	0	1/103 (1.0%)	0	0
Most common AEs				
Fatigue	19/155 (12.3%)	21/103 (20.4%)	8/58 (13.8%)	[redacted]
Headache	22/155 (14.2%)	21/103 (20.4%)	7/58 (12.1%)	[redacted]
Nausea	23/155 (14.8%)	11/103 (10.7%)	6/58 (10.3%)	[redacted]
Insomnia	[redacted]	[redacted]	3/58 (5.2%)	[redacted]
AEs of special interest				
Rash (any type)	10/155 (6.5%)	16/103 (15.5%)	10/58 (17.2%)	3/28 (10.7%)
Pruritus	7/155 (4.5%)	14/103 (13.6%)	6/58 (10.3%)	4/28 (14.3%)
Photosensitivity	2/155 (1.3%)	5/103 (4.9%)	3/58 (5.2%)	2/28 (7.1%)
Dyspnoea	3/155 (1.9%)	3/103 (2.9%)	1/58 (1.7%)	[redacted]
Increased bilirubin	1/155 (0.6%)	2/103 (1.9%)	4/58 (6.9%)	0
Anaemia	[redacted]	[redacted]	1 (1.7%)	0

AE = adverse events.

[a] Study 3017 only included non-cirrhotic patients.

[b] Only AEs in the SMV12+SOF12 treatment arm are included in the table.

[c] Study 3018 only included patients with cirrhosis

[d] Pearlman 2015 and Study 3018 only included patients with cirrhosis

Source: Table Bi.29 and Table Bi.30, pp81-82 of the submission; Pearlman 2015; COSMOS CSR Tables 22, 23, 24, 26 and 27, pp41-47 Study 3017 Results; Tables 22, 23, 27 and 28 pp37-43 Study 3018 Results.

6.18 As there were limited safety data for DCV+SOF in genotype 1 HCV patients (n=62), only a comparison of the safety data for SMV+SOF and LDV/SOF is presented below. The most commonly reported AEs in both the SMV+SOF studies and the LDV/SOF studies were fatigue, headache and nausea. The incidence of skin events, including rash, pruritus and photosensitivity, was higher in patients treated with SMV+SOF compared to LDV/SOF. However, the majority of the skin events observed in patients treated with SMV+SOF were of mild to moderate severity. Otherwise, there were no clear differences between the safety profiles of the two treatment regimens.

Table 6: Summary of key adverse events for SMV12+SOF12 and LDV/SOF

	Study 3017 n/N (%)	Study 3018 n/N (%)	ION-3 LDV/SOF[a] n/N (%)	ION-1 LDV/SOF12 n/N (%)	ION-2 LDV/SOF12 n/N (%)
Population	TN and TE Non-cirrhotic	TN and TE 100% cirrhotic	TN Non-cirrhotic	TN 16% cirrhotic	TE 20% cirrhotic
Any AE	103/155 (66%)	72/103 (70%)	294/431 (68%)	169/214 (79.0%)	73/109 (67%)
Any serious AE	1/155 (1%)	5/103 (5%)	9/431 (2%)	1/214 (0.5%)	0
Number discontinued	0	3/103 (3%)	2/431 (<1%)	0	0
Number died	0	1/103 (1%)	0	0	0
Most common AEs					
Fatigue	19/155 (12%)	21/103 (20%)	94/431 (22%)	44/214 (20.6%)	23/109 (21%)
Headache	22/155 (14%)	21/103 (20%)	63/431 (15%)	53/214 (25%)	28/109 (26%)
Nausea	23/155 (15%)	11/103 (11%)	39/431 (9%)	24/214 (11%)	13/109 (12%)
Rash (any type)	10/155 (6%)	16/103 (16%)	8/431 (2%)	16/214 (7%)	2/109 (2%)
Pruritus	7/155 (5%)	14/103 (14%)	7/431 (2%)	11/214 (5%)	NR
Photosensitivity	2/155 (1.3%)	5/103 (4.9%)	NR	NR	NR
Insomnia	[redacted]	[redacted]	26/431 (6%)	17/214 (8%)	10/109 (9%)
Diarrhoea	[redacted]	NR	24/431 (6%)	24/214 (11%)	7/109 (6%)
Irritability	NR	NR	12/431 (3%)	11/214 (5%)	2/109 (2%)
Asthenia	NR	NR	NR	14/214 (7%)	NR
Cough	[redacted]	NR	10/431 (2%)	6/214 (3%)	5/109 (5%)
Arthralgia	[redacted]	NR	25/431 (6%))	NR	7/109 (6%)

AE = adverse event; LDV = ledipasvir; NR = not reported; SMV = simeprevir; SOF = sofosbuvir; TE = treatment-experienced; TN = treatment-naïve

[a] Combined LDV/SOF 8 and LDV/SOF 12 treatment arms

Source: Table Bii.6.5 p146 and Table Bii.6.8 p148 of the submission; Study 3017 and Study 3018 Topline Results; Afdhal *et al* (2014)[6, 7] and Kowdley *et al* (2014)[8]

Benefits/harms

6.19 A summary of the comparative benefits and harms for SMV+SOF versus 'no treatment' is presented in the following table, based on the evidence provided in the submission.

Table 7: The benefit/harm of SMV+SOF compared with no treatment

Patient group	Comparison	Benefits/harms
Genotype 1, treatment naïve, non-cirrhotic patients	for every 100 patients treated with SMV+SOF for 12 weeks in comparison to no treatment	• Approximately 97 additional patients would be expected to achieve an SVR; and • Approximately 1 additional patient would experience a serious adverse event.
Genotype 1, treatment naïve, cirrhotic patients	for every 100 patients treated with SMV+SOF for 12 weeks in comparison to no treatment:	• Approximately 88 additional patients would be expected to achieve SVR; and • Approximately 5 additional patients would experience a serious adverse event.
Genotype 1, treatment experienced, non-cirrhotic patients	for every 100 patients treated with SMV+SOF for 12 weeks in comparison to no treatment:	• Approximately 95 additional patients would be expected to achieve an SVR, and • Approximately 1 additional patient would experience a serious adverse event.
Genotype 1, treatment experienced, cirrhotic patients	for every 100 patients treated with SMV+SOF for 12 weeks in comparison to no treatment:	• Approximately 79 additional patients would be expected to achieve an SVR, and • Approximately 5 additional patients would experience a serious adverse event

Note: Efficacy results were based on Studies 3017 and 3018, which were relatively large studies and more representative of the proposed PBS population than Pearlman 2015 and COSMOS.
Safety results for non-cirrhotic patients were based on Study 3017, while results for cirrhotic patients were based on Study 3018. Both treatment-naïve and treatment-experienced patients were combined in these analyses.

6.20 There were no clear differences in the benefits and harms of SMV+SOF compared to LDV/SOF.

Clinical claim

6.21 The submission described SMV+SOF as superior in terms of efficacy and inferior in terms of safety compared with no treatment. Based on the evidence provided in the submission, the PBAC considered this claim was reasonable.

6.22 The submission described SMV+SOF as similar in terms of efficacy and safety to other interferon-free treatment regimens. The SVR12 rates in both treatment-naïve and treatment-experienced patients without cirrhosis were consistently high and reasonably similar for each of the alternative interferon-free treatment regimens. As the confidence intervals of the SVR12 rates for each treatment regimen in cirrhotic patients were generally wider than those in non-cirrhotic patients, any interpretation of the comparison between treatment regimens in these patients would be more uncertain. The results from Study 3018 suggested that SMV12+SOF12 may be inferior to Viekira PAK-RBV in treatment experienced patients with cirrhosis. However, the high SVR12 rate observed in Pearlman 2015 for this patient subgroup (33/36, 91.7%) suggested a similar treatment effect to other interferon-free treatment regimens. The incidence of skin events (including rash, pruritus and photosensitivity) was higher in patients treated with SMV+SOF compared to LDV/SOF; most events were of mild to moderate severity. Otherwise, there were no clear differences between the safety profiles of SMV+SOF and LDV/SOF.

6.23 The ESC agreed with the submission that SMV+SOF is similar in terms of efficacy and safety to other interferon-free treatment regimens.

6.24 Though the submission presented unadjusted comparison of SVR results, the PBAC considered that it was reasonable to accept that a course of SMV+SOF was non-inferior for comparative efficacy with a course of LDV/SOF, DCV+SOF or Viekira PAK/Viekira PAK-RBV for treatment of Genotype 1 CHC.

6.25 Based on the available data, the Committee considered that it was reasonable to consider that a course of SMV+SOF had a similar safety profile as the ribavirin-free course of LDV/SOF, DCV+SOF and Viekira PAK.

Economic analysis

6.26 The submission presented a modelled cost-utility analysis of SMV+SOF compared with a mixture of no treatment ([redacted]%) and SMV+PR ([redacted]%). The submission presented an incremental cost-effectiveness ratio (ICER) weighted by the comparator treatment and by patients' disease severity at baseline. 'No treatment' has been accepted by the PBAC as the appropriate comparator for all-oral, interferon-free HCV regimens (5.17 Sofosbuvir PSD, July 2014 PBAC meeting). The evaluation presented a cost-utility analysis of SMV+SOF versus no treatment only.

6.27 The Pre-Sub-Committee Response (PSCR, p1) requested that IFN-free SIM+SOF be considered on a cost-minimisation basis with the LDV/SOF and DAC+SOF, recommended at the March 2015 PBAC meeting. Given the clinical outcomes, the ESC considered that it was appropriate to consider that the price of a course of treatment should be the same as the price of a course of treatment with other high efficacy/ low toxicity IFN-free treatments.

6.28 In the submission, the model captured both on-treatment and off-treatment phases. Patients entered the model at 50 years of age. Patients were stratified by baseline liver disease (mild CHC, moderate CHC and cirrhosis). Treatment effects were incorporated into the model in the form of SVR rates. If patients achieved an SVR from treatment, they transitioned to a lifetime free of HCV (with a small risk of re-infection ([redacted]%) and limited transition ([redacted]%) from compensated cirrhotic disease with SVR to a hepatocellular carcinoma health state). If patients did not receive any treatment or HCV treatment failed, they would move on to a lifetime with HCV. The evaluation was structured as a Markov state-transition model with eleven health states, that described the progression of disease over the lifetime.

Table 8: Summary of model structure and rationale

Time horizon	36 weeks (short-term model) plus 50 years (long-term model). The time horizon of the long-term model was longer than the PBAC's recommended 30-year time horizon (5.17 Sofosbuvir PSD, July 2014 PBAC meeting).
Outcomes	Quality adjusted life years (QALYs).
Methods used to generate results	Two distinct phases: 1) Short-term decision analytic model; and 2) Long-term Markov model with 11 mutually exclusive health states describing progression of the disease over a lifetime. Cohort expected value analysis.
Cycle length	1 year for the long-term Markov model
Transition probabilities	Based on literature review.
Discount rate	5% for costs and outcomes
Software package	Microsoft Excel 2010

PSD = Public Summary Document.

6.29 The SVR rates used in the submission's economic model were taken from the COSMOS study. The number of patients in COSMOS was too small to reliably estimate the SVR rates in the target population. During the evaluation, SVR data from the two larger studies, 3017 and 3018, were available and were used as model inputs.

6.30 Disease severity and history of prior HCV treatments are both important prognostic factors and treatment effect modifiers. The submission did not present the results of the economic evaluation by subpopulation (ie treatment-naïve non-cirrhotic, treatment-naïve cirrhotic, treatment-experienced non-cirrhotic and treatment-experienced cirrhotic). Rather, an identical SVR rate ([redacted]%) was assumed for all these subpopulations. Efficacy data from Studies 3017 and 3018 showed that SMV+SOF was less effective (associated with a lower rate of SVR) in cirrhotic subgroups. In addition, there was a trend for a lower SVR rate in treatment-experienced cirrhotic patients than in treatment-naïve cirrhotic patients. Individual ICERs for each of the subpopulations were presented in the Commentary.

6.31 Key drivers of the model are summarised in the table below.

Table 9: Key drivers of the model

Description	Method/Value	Impact
Transition probabilities between early health states in HCV infection (from mild to moderate HCV and from moderate HCV to compensated cirrhosis)	The transition probabilities, which were identical to those used in the telaprevir submission considered by the PBAC at the March 2012 meeting, were sourced from older longitudinal studies and likely to be overestimates. The PBAC noted, when considering telaprevir, that these were likely to result in an overestimation of the cost effectiveness of telaprevir. A sensitivity analysis was conducted during the evaluation using the NICE transition probabilities between earlier health states[9, 10].	High, favours SMV+SOF
Time horizon	50 years. This was considerably longer than the PBAC recommendation of a 30-year time horizon when considering other HCV models (5.17 Sofosbuvir PSD, July 2014 PBAC meeting).	Moderate, favours SMV+SOF
The proportion of patients with mild CHC	The submission assumed [redacted]% of patients had mild CHC and the remaining [redacted]% had moderate CHC. The proportion of patients with mild CHC was a likely underestimate, as two recent published papers[11, 12] have estimated the ratio of mild versus moderate CHC to be 70% versus 30%. These proportions were used in a sensitivity analysis performed during the evaluation.	Moderate, favours SMV+SOF
Utility gain due to achieving an SVR	The submission assumed utility gains of [redacted]-[redacted] due to SVR. These were identical to those used in the previous telaprevir model considered by the PBAC at the March 2012 meeting. The PBAC considered that this was a source of uncertainty. The assumption of [redacted] utility increments due to SVR for cirrhotic patients was noticeably higher than the 0.05-0.06 utility increments used in earlier CHC models[9, 10]. A recent study showed that SVR was associated with an improved EQ-5D index of 0.041(±0.010) units (P < 0.0001). This estimate was accepted by NICE[13]. A sensitivity analysis using a utility gain of 0.041 was performed during the evaluation.	Moderate, favours SMV+SOF

SMV = simeprevir; SOF = sofosbuvir; HCV = hepatitis C virus; CHC = chronic hepatitis C; NICE = National Institute for Health and Care Excellence; SVR = sustained virologic response.

6.32 The ESC noted that submission used a number of assumptions and model inputs that consistently favoured SMV+SOF:

- Transition probabilities between early health states in HCV infection (from mild to moderate HCV and from moderate HCV to compensated cirrhosis) were identical to those used in the telaprevir submission considered at the March 2012 PBAC meeting. The PBAC noted that these transition probabilities were likely to result in an overestimation of the cost-effectiveness of telaprevir (Telaprevir Public Summary Document (PSD), March 2012 PBAC meeting);
- A 50-year time horizon - considerably longer than the PBAC's advice that

a 30-year time horizon should be used (5.17 Sofosbuvir, PSD, July 2014 PBAC meeting);

- The proportion of patients with mild chronic hepatitis C (CHC) entering the model was a likely underestimate ; and
- Utility increments ([redacted]) due to SVR that were identical to those used in the previous telaprevir submission and likely to be overestimated. The PBAC considered that this was a source of uncertainty when considering telaprevir (Telaprevir PSD, November 2011 PBAC meeting).

6.33 As the price for sofosbuvir alone was not known to the sponsor, it was not possible to determine the cost of SMV+SOF therapy in the requested population in the submission. The base case economic evaluation assumed a total regimen cost of [redacted] per 12-week course of SMV+SOF treatment and was performed relative to a mixed comparator. The results of the economic analyses conducted during the evaluation - based on this assumed price, relative to no treatment and using the SVR rates observed in Studies 3017 and 3018 - are summarised below.

Table 10: Results of the economic evaluation by subpopulations[a]

	SMV+SOF	No treatment	Increment
Treatment-naïve, non-cirrhotic			
Costs	$[redacted]	$[redacted]	$[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Incremental cost/extra QALY gained			**$[redacted]**
Treatment-naïve, cirrhotic			
Costs	$[redacted]	$[redacted]	$[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Incremental cost/extra QALY gained			**$[redacted]**
Treatment-experienced, non-cirrhotic			
Costs	$[redacted]	$[redacted]	$[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Incremental cost/extra QALY gained			**$[redacted]**
Treatment-experienced, cirrhotic			
Costs	$[redacted]	$[redacted]	$[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Incremental cost/extra QALY gained			**$[redacted]**

QALY = quality-adjusted life year; SMV = simeprevir; SOF = sofosbuvir

[a] SVR results from Study 3017 and Study 3018 are used in the economic evaluation

6.34 Results of key sensitivity analyses performed during the evaluation for the treatment-naïve, non-cirrhotic population are summarised below. The treatment-naïve, non-cirrhotic subgroup was selected, as this represents the majority of the proposed PBS population.

Table 11: Results of additional sensitivity analyses performed during the evaluation[a]

Univariate analyses	Assumption	Incremental costs	Incremental QALYs	ICER
Base case		$[redacted]	[redacted]	$[redacted]
Time horizon (base case: 50 years)	#1: 30 years	$[redacted]	[redacted]	$[redacted]
% of patients with mild CHC (base case: 47% (the remaining 53% with moderate CHC))	#2: 70% (the remaining 30% with moderate CHC, as estimated in Dore et al 2014 and Sievert et al 2014[11, 12])	$[redacted]	[redacted]	$[redacted]
Transition probability between early health states (base case: mild to moderate: 0.041; moderate to severe: 0.073)	#3: The lowest estimates in the literature (mild to moderate: 0.025; moderate to cirrhosis: 0.010)	$[redacted]	[redacted]	$[redacted]
	#4: NICE estimates (mild to moderate: 0.025; moderate to cirrhosis: 0.037)	$[redacted]	[redacted]	$[redacted]
Utility gain due to SVR (base case: 0.05-0.11)	#5: 0	$[redacted]	[redacted]	$[redacted]
	#6: 0.041 (as accepted by the NICE)	$[redacted]	[redacted]	$[redacted]
Multivariate analysis[b] (#1 & #2 & #4 & #6)		**$[redacted]**	[redacted]	**$[redacted]**

CHC = chronic hepatitis C; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; SVR = sustained virologic response; [a] SVR result from Study 3017 (97.4%) is used in the analysis

6.35 The relationship between the ICER and the price of a 12-week SMV+SOF treatment was explored for the base case and a sensitivity analysis, using the assumptions/inputs in the multivariate sensitivity analysis presented above in Table 10. The results indicated that the ICER in the sensitivity analysis would vary from less than $15,000 per quality-adjusted life year (QALY) to $45,000 to $75,000 QALY, if the regimen price varied from ($15,000-$45,000) to ($45,000- $75,000). The ESC noted that a large opportunity cost for all-oral interferon-free HCV regimens, including SMV/SOF, is expected. The listing of interferon-free HCV regimens would potentially reduce access to future cost-effective medicines. Given this, at the March 2015 PBAC meeting, the PBAC advised that new interferon-free regimens would be cost-effective at $15,000/QALY, the lower end of the ICER range that PBAC has accepted for telaprevir or boceprevir.

Figure 2: Relationship between total regimen cost and the ICER for treatment-naïve, non-cirrhotic patients[a, b]

[THIS FIGURE HAS BEEN REDACTED]

6.36 While noting the sponsor's proposal of a cost-minimisation analysis in the PSCR and reiterated in the pre-PBAC response, the PBAC disagreed with the sponsor's discussion about the inputs and assumptions in the economic model presented in the submission. Overall, this economic model favoured SMV and that applying more conservative inputs or scenarios increased the ICERs/QALY to a range higher than the PBAC considered cost-effective for the treatment of CHC.

6.37 The PBAC considered a cost-minimisation was appropriate, as the clinical evidence presented in the submission suggested that there is no basis on which to consider

that one course of SMV+ SOF was more effective than a course of treatment with other high efficacy/ low toxicity IFN-free regimen. The cost-minimisation analysis and restriction will depend on the conditions set out in the final product information. The PBAC recalled from the March 2015 meeting, in consideration of CHC treatments, that:

- the cost of the entire treatment course should include the wholesale and pharmacy mark ups and dispensing fees associated with a General Schedule listing.
- the cost to achieve a SVR12 should be independent of the treatment duration and treatment dose considered to be appropriate to achieve a SVR in patients.
- the listing of DCV+SOF was recommended on the basis of acceptable cost effectiveness over no treatment, however the PBAC recommended that the price of a course of treatment should be the same as the price of a course of treatment with ledipasvir/sofosbuvir.

Drug cost/patient/course

6.38 Cost of SMV+SOF: $[redacted] for a 12 week course.
As the cost of sofosbuvir is not known, an assumed price for SMV+SOF was used in the submission. The cost of simeprevir was $[redacted] (Public) and $[redacted] (Private) for a 12 week course, based on the current DPMQs for simeprevir listed on the PBS.

Estimated PBS usage & financial implications

6.39 This submission was not considered by DUSC.
The submission used an epidemiological approach to estimate the financial implications of listing simeprevir for use in combination with sofosbuvir for treatment of genotype 1 CHC. The prevalence and current treatment rate of HCV infection, sourced from the Kirby Institute Annual Surveillance Report (2001-2014), as well as data reported in advice from the Australian Liver Association (November 2014)[1], were used to project the number of patients likely to be treated over the first five years of listing. The submission assumed that the number of patients treated each year would increase by [redacted]%, due to increases in clinic treatment capacity resulting from the reduced treatment duration and superior safety profile of interferon-free regimens. It was also assumed that, from Year 2 of listing, the treatment rate would increase by a further [redacted]% due to improved clinic efficiency resulting from familiarity with the new regimens. The financial implications were based on the assumption that no other all-oral, interferon-free treatment regimens were listed on the PBS; SMV+SOF was assumed to have a [redacted]% market share once listed. The submission assumed that, in the absence of SMV+SOF, the number of patients treated would remain constant at the current estimate of [redacted] genotype 1 patients treated per year. As both LDV/SOF and DCV+SOF were approved for listing at the March 2015 PBAC Meeting, it is unlikely that SMV+SOF will have [redacted]% market share for treatment of genotype 1 CHC patients if all are listed.

[1] Recommendations from the Australian Liver Association on patients with a high clinical need for treatment with all oral regimes for chronic hepatitis C, November 2014.

6.40 At the February 2015 DUSC meeting in consideration of LDV/SOF, SOF+PR and DCV+SOF, based on the treatment target set in the Fourth National Hepatitis C strategy 2014-2017 (NHCS), the DUSC estimated that the number of patients of all genotypes that would be treated over the first five years of listing of interferon-free treatment regimens, would be 6,600 in Year 1, 9,900 in Year 2 and 15,000 in Years 3-5. The financial implications to the PBS and the MBS, based on the DUSC estimates, were recalculated during the evaluation, assuming that 54.5% of treated patients had genotype 1 HCV infection[2] (NHCS-based estimates).

Table 12: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number likely to be treated[a] NHCS-based estimates					
Market share	%	%	%	%	%
Scripts[b] NHCS-based estimates					
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS NHCS-based estimates	$ $	$ $	$ $	$ $	$ $
Net cost to MBS NHCS-based estimates	$ $	$ $	$ $	$ $	$ $
Estimated total net cost					
Net cost to PBS/RPBS/MBS NHCS-based estimates	**$** **$**	**$** **$**	**$** **$**	**$** **$**	**$** **$**

[a] Total number of patients treated over 5 years: ; *NHCS-based estimate 33,300 patients over 5 years.*

[b] Assuming 2 scripts for simeprevir and 3 scripts for sofosbuvir per patient, as estimated by the submission.

Note: NHCS-based estimates assume 4,400 patients of all genotypes were treated in 2014, the number treated increases by 50% each year for years 1-3, and 54.5% of patients treated have genotype 1 HCV infection, consistent with the assumptions used in the DUSC estimates for LDV/SOF, SOF+PR and DCV+SOF.

Source: Table E.11, p 239 and E.24, p246 of the Submission

The redacted table above shows that the estimated number of scripts would be 10,000 – 50,000 per year and the net cost to Government would be more than $100 million per year.

6.41 The estimated PBS usage and financial implications were highly uncertain. Key uncertainties included:

- The cost of sofosbuvir is unknown and an assumed price is used in the submission;
- The number of patients likely to be treated per year, given
  - There is a large pool of people living with CHC infection (230,000); however there are constraints on the capacity of the health system to manage HCV;
  - The submission's estimate of the likely number of patients treated over the first 5 years of listing was less than the number of patients estimated by DUSC at the February 2015 meeting;
  - The number of patients who are deferring treatment to receive interferon-free therapy is unknown; and

[2] Consistent with the Recommendations from the Australian Liver Association on patients with a high clinical need for treatment with all oral regimes for chronic hepatitis C, November 2014

  - The estimates were based on a Section 100 (HSD) listing, originally requested by the sponsor, while the PBAC have recommended general schedule listing for interferon-free treatments.
- The market share of alternative interferon-free regimens listed for treatment of genotype 1 HCV.

Quality Use of Medicines

6.42 The submission claimed that the sponsor is committed to ensuring optimal health outcomes for patients by collaborating with healthcare professionals and consumers. The submission has indicated that education and resources regarding SMV+SOF treatment would be delivered to those involved in the care and management of a patient who is prescribed simeprevir.

Financial Management – Risk Sharing Arrangements

6.43 The sponsor indicated they would be willing to work with the Department of Health to negotiate a Deed of Agreement to address the uncertainty regarding the number of patients who would be treated with all-oral, interferon-free HCV regimens if they are listed on the PBS.

6.44 The PBAC recalled from the March 2015 meeting, in consideration of CHC treatments that the Committee recommended a Risk Share Arrangement. 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.

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

7 PBAC Outcome

7.1 The PBAC recommended deferral of the submission given that a positive TGA Delegate's Overview was not available at the time of consideration. The PBAC was of a mind to recommend listing of simeprevir, in combination with sofosbuvir, but decided to wait for finalisation of the TGA registration process to determine the circumstances of listing.

7.2 The PBAC considered that the conditions and circumstances of the listing of simeprevir in combination with peginterferon alfa and ribavirin should be reassessed to align this listing with a listing in combination with sofosbuvir.

Outcome:
Deferred.

8 Context for decision

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

PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

Janssen are continuing to work towards achieving a PBS listing for simeprevir as an interferon-free combination with sofosbuvir for genotype 1 Hepatitis C virus infection.