5.16 SIMEPREVIR, 150 mg capsule, Olysio®, Janssen-Cilag Pty Ltd.

1 Purpose of Application

1.1 To request a Section 100 (Highly Specialised Drugs Program) listing for simeprevir, in combination with peg-interferon + ribavirin (PR), to treat hepatitis C virus (HCV) genotype 1 infection.

2 Requested listing

2.1 The requested restriction is briefly summarised below:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
SIMEPREVIR Capsule 150mg, 7 capsules	6	0	OLYSIO®	Janssen-Cilag Pty Ltd

Section 100 (Highly Specialised Drug Program)

Private Hospital Authority Required; Public Hospital Authority Required (STREAMLINED)

1) Chronic genotype 1 hepatitis C infection;
2) Patient may either: a) not have received prior treatment with interferon alfa or peginterferon alfa for hepatitis C; or b) have received prior treatment with interferon alfa or peginterferon alfa for hepatitis C;
3) The treatment must be in combination with peginterferon alfa and ribavirin;
4) Patients who have received prior treatment with a NS3/4A protease inhibitor are not eligible to receive PBS-subsidised simeprevir, except where the patient has developed intolerance to the other NS3/4A protease inhibitor of a severity necessitating treatment withdrawal;
5) The treatment with simeprevir must be limited to a maximum duration of 12 weeks; and

The treatment must cease if the results of an HCV RNA quantitative assay at week 4 show that the plasma HCV RNA is equal or greater than 25 IU/mL.

2.2 The ESC noted that the commentary stated that the Q80K polymorphism appears to be an effect modifier for simeprevir + PR. The Pre-Sub-Committee Response (PSCR) stated that the prevalence of the Q80K polymorphism in Australia is low [redacted] compared to its prevalence (close to 50%) in US patients with HCV genotype 1a. The ESC agreed with the PSCR that screening for Q80K polymorphism in Australia would not be necessary provided the proportion of patients with the Q80K polymorphism does not increase significantly over time.

2.3 The ESC noted that simeprevir and sofosbuvir (a NS5B polymerase inhibitor) may be used together as an interferon-free treatment option on the basis of emerging evidence for this regimen (COSMOS Phase II) and the recent recommendation in the American Association for the Study of Liver Disease (AASLD) updated guidelines for treatment-naïve patients with HCV genotype 1 who are not eligible to receive IFN.

2.4 The basis for requested listing is cost-minimisation to telaprevir (TEL) and boceprevir (BOC).

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

3 Background

3.1 The submission was made under TGA/PBAC Parallel Process. Simeprevir received a positive recommendation at the ACPM meeting on 6 Jun 2014.

3.2 This drug has not been considered by PBAC previously

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.

4.2 Currently, the PBS reimburses Direct Acting Antivirals (DAAs), including boceprevir and telaprevir (both of which must be used in combination with PR), for the treatment of HCV Genotype 1. Approximately 50% of patients in Australia are infected with Genotype 1.

4.3 Simeprevir is an HCV NS3/4A protease inhibitor and an alternative DAA treatment option for patients who are treatment naïve and for patients who have previously been treated with peginterferon alfa. Patients who fail prior therapy with a protease inhibitor (simeprevir, telaprevir or boceprevir) are not allowed to be re-treated with another protease inhibitor unless they discontinued the previous protease inhibitor because of drug intolerance.

4.4 The ESC noted the likely treatment algorithm for HCV is changing rapidly, particularly with the development of interferon-free regimens. The ESC considered that the decision making process should be framed in this evolving treatment landscape. Patients with HCV Genotype 1 may not immediately seek treatment for HCV disease because:

- Patients may be avoiding treatment due to the adverse side effect profile of telaprevir or boceprevir
- Many patients, particularly those with no or little liver fibrosis, are likely to be waiting for short course and/or IFN-free treatments.

4.5 The ESC noted that in the Public Summary Document of the recent stakeholder meeting of new Hepatitis C antiviral drugs (February 2014) that only 41% of all patients with HCV Genotype 1 were treated with direct acting antivirals.

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

5 Comparator

5.1 The ESC considered that telaprevir and boceprevir are the appropriate comparators.

5.2 The PBAC considered that telaprevir and boceprevir were appropriate comparators on the basis that they are pharmacological analogues, and are the therapies most likely to be replaced in Australia at the time of consideration of the submission. However, the PBAC noted that the likely treatment algorithm for HCV is changing rapidly, particularly with the development of interferon-free regimens. As an example of the rapidly evolving treatment landscape, both telaprevir and boceprevir are now not recommended for the treatment of patients with HCV genotype 1 in the guidelines

of the AASLD and the Infectious Disease Society of America. The PBAC noted that over 30 DAAs are in clinical development, including inhibitors of NS5A, NS5B and NS3/4A as well as host-targeting antivirals.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (261), health care professionals (25) and organisations (24) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with the new drugs for HCV being considered by the PBAC, including turning an infection from a chronic disease to one that can be cured, with a shorter treatment regimen, reduced side effects, and a broader access to treatment.

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

Clinical trials

6.3 A summary of the trials presented in the submission is in the table below.

Trial ID	Description	Publication citation
Treatment Naïve		
Indirect comparison		
Simeprevir		
QUEST-1 (Study C208)	Multi-centre, phase III, randomised, double-blind, placebo-controlled	Clinical study report: Primary analysis: A Phase III, randomized, double-blind, placebo-controlled study to investigate the efficacy, safety and tolerability of TMC435 vs. placebo as part of a treatment regimen including peginterferon α-2a and ribavirin in treatment-naïve, genotype 1 hepatitis C-infected subjects. February 2013. Topline results: Final analysis: A Phase III, randomized, double-blind, placebo-controlled study to investigate the efficacy, safety and tolerability of TMC435 vs. placebo as part of a treatment regimen including peginterferon α-2a and ribavirin in treatment-naïve, genotype 1 hepatitis C-infected subjects. May 2013.
QUEST-2 (Study C216)	Multi-centre, phase III, randomised, double-blind, placebo-controlled	Clinical study report: Primary analysis: A Phase III, randomized, double-blind, placebo-controlled study to investigate the efficacy, safety and tolerability of TMC435 versus placebo as part of a treatment regimen including peginterferon α-2a (Pegasys®) and ribavirin (Copegus®) or peginterferon α-2b (PegIntron®) and ribavirin (Rebetol®) in treatment-naïve, genotype 1, hepatitis C-infected subjects. February 2013. Topline results: Final analysis: A Phase III, randomized, double-blind, placebo-controlled study to investigate the efficacy, safety and tolerability of TMC435 versus placebo as part of a treatment regimen including peginterferon α-2a (Pegasys®) and ribavirin (Copegus®) or peginterferon α-2b (PegIntron®) and ribavirin (Rebetol®) in treatment-naïve, genotype 1, hepatitis C-infected subjects. May

Trial ID	Description	Publication citation
		2013.
PILLAR (Study C205)	Phase IIb, randomised, double-blind, placebo-controlled	Clinical study report: A Phase IIb, randomized, double-blind, placebo-controlled trial to investigate the efficacy, tolerability, safety and pharmacokinetics of TMC435 as part of a treatment regimen including peginterferon alfa 2a and ribavirin in treatment-naïve genotype 1 hepatitis C infected subjects. March 2012. Lenz, O, Fevery, B, et al. TMC435 in combination with peginterferon alpha-2A/ribavirin in treatment-naive patients infected with HCV genotype 1: Virology analysis of the pillar study. Hepatology 2011; 54: 985A. Fried, MW, Buti, M, et al. Once-daily simeprevir (TMC435) with pegylated interferon and ribavirin in treatment-naive genotype 1 hepatitis C: The randomized PILLAR study. Hepatology 2013; 58(6): 1918-1929.
Telaprevir		
ADVANCE	Multi-centre, Phase III, randomised, double-blind, placebo-controlled	Jacobson, IM, McHutchison, JG, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. New England Journal of Medicine 2011; 364(25): 2405-2416.
Boceprevir		
SPRINT-2	Multi-centre, Phase III, randomised, double-blind, placebo-controlled	Poordad, F, McCone, J Jr, et al. Boceprevir for untreated chronic HCV genotype 1 infection. New England Journal of Medicine 2011; 364(13): 1195-1206. Poordad, F, McCone, J Jr, et al. Boceprevir (BOC) combined with peginterferon ALFA-2B/ribavirin (P/R) for treatment-naive patients with hepatitis C virus (HCV) genotype (G) 1: Sprint-2 final results. Hepatology 2010; 52: 402A-403A. Sulkowski, MS, Poordad, F, et al. Boceprevir combined with peginterferon alfa-2b/ribavirin for previously untreated patients with hepatitis C virus genotype 1: SPRINT-2 final results. Journal of the International Association of Physicians in AIDS Care 2011; 10(3): 197-198.
Treatment experienced		
Direct trial		
ATTAIN	Multi-centre, phase III, randomised, double-blind, head-to-head	Clinical trial protocol amendment II: A phase III, randomized, double-blinded trial to evaluate the efficacy, safety and tolerability of TMC435 vs telaprevir, both in combination with PegIFN α-2a and ribavirin, in chronic hepatitis C genotype-1 infected subjects who were null or partial responders to prior PegIFN α-2a and ribavirin therapy. May 2012. Topline results: Week 60 interim analysis: A phase III, randomized, double-blinded trial to evaluate the efficacy, safety and tolerability of TMC435 vs telaprevir, both in combination with PegIFN α-2a and ribavirin, in chronic hepatitis C genotype-1 infected subjects who were null or partial responders to prior PegIFN α-2a and ribavirin therapy. March 2014.
Indirect comparison		
Simeprevir		
PROMISE (Study HPC3007)	Multi-centre, phase III, randomised, double-blind, placebo-controlled	Clinical study report: Primary analysis: A Phase III, randomized, double-blind, placebo-controlled study to investigate the efficacy, safety and tolerability of TMC435 vs. placebo as part of a treatment regimen including peginterferon α-2a and ribavirin in hepatitis C, genotype 1 infected subjects who relapsed after previous interferon-based therapy. February 2013.

Trial ID	Description	Publication citation
		Topline results: Final analysis: A Phase III, randomised, double-blind, placebo-controlled study to investigate the efficacy, safety and tolerability of TMC435 vs. placebo as part of a treatment regimen including peginterferon α-2a and ribavirin in hepatitis C, genotype 1 infected subjects who relapsed after previous interferon-based therapy. May 2013.
ASPIRE (Study C206)	Phase IIb, randomised, 7-arm, double-blind, placebo-controlled	Clinical study report: A Phase IIb, randomised, double-blind, placebo-controlled trial to investigate the efficacy, tolerability, safety and pharmacokinetics of TMC435 as part of a treatment regimen including PegIFN α-2a and ribavirin in HCV genotype 1 infected subjects who failed to respond or relapsed following at least 1 course of PegIFNα-2a/b and RBV therapy. July 2012. Zeuzem, S, Berg, T, et al. Simeprevir increases rate of sustained virologic response among treatment-experienced patients with HCV genotype-1 infection: A phase IIb trial. Gastroenterology 2014; 146(2): 430-441.
Telaprevir		
REALIZE	Phase III, randomised, double-blind, placebo-controlled	Zeuzem, S, Andreone, P, et al. Telaprevir for retreatment of HCV infection. New England Journal of Medicine 2011. 364(25): 2417-2428. Zeuzem, S, Andreone, P, et al. Realize trial final results: Telaprevir-based regimen for genotype 1 hepatitis c virus infection in patients with prior null response, partial response or relapse to peginterferon/ribavirin. Journal of Hepatology 2011; 54: S3. Pockros, P, Zeuzem, S, et al. Telaprevir-based regimen in genotype 1 hepatitis C virus-infected patients with prior null response, partial response or relapse to peginterferon/ribavirin: REALIZE trial final results. Gastroenterology 2011; 140(5): S898.
Boceprevir		
Trial 5685	Multi-centre, Phase III, randomised, double-blind, placebo-controlled	Flamm, SL, Lawitz, E, et al. Boceprevir with peginterferon alfa-2a-ribavirin is effective for previously treated chronic hepatitis C genotype 1 infection. Clinical Gastroenterology and Hepatology 2013; 11(1): 81-87.
RESPOND-2	Phase III, randomised, double-blind, placebo-controlled	Bacon, BR, Gordon, SC, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. New England Journal of Medicine 2011; 364(13): 1207-1217. Poordad, F, Bacon, B, et al. Boceprevir combined with peginterferon alfa-2b/ribavirin for treatment-experienced patients with hepatitis C Virus (HCV) genotype-1: RESPOND-2 final results. Hepatology International 2011; 5(1): 13. Sulkowski, MS, Bacon, BR, et al. Boceprevir combined with peginterferon alfa-2b/Ribavirin for previous treatment failure patients with hepatitis C virus genotype 1: RESPOND-2 final results. Journal of the International Association of Physicians in AIDS Care 2011; 10(3): 198.

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

Comparative effectiveness and harms

6.4 TREATMENT NAÏVE – INDIRECT COMPARISON:

Results of sustained virologic response (absence of detectable RNA of the hepatitis C virus 24 weeks after completion of antiviral therapy: SVR24) across trials including treatment naïve patients are presented in the submission. The PBAC accepted the relevance of SVR24 as a surrogate outcome while listing telaprevir and boceprevir.

Trial ID	SMV + PR vs placebo + PR			TVR/BOC + PR vs placebo + PR			Indirect comparison OR[d] [95% CI]
	OR[a] [95% CI]	SMV12+PR24/48 n/N (%)	PR48[b] n/N (%)	PR48[b] n/N (%)	Comparator n/N (%)	OR[c] [95% CI]	
QUEST-1	4.01 [2.54, 6.30]	210/264 (79.5%)	64/130 (49.2%)	–	–	–	SMV+PR vs TVR+PR: 0.97 [0.62, 1.51] SMV+PR vs BOC+PR: 1.26 [0.81, 1.93]
QUEST-2	4.14 [2.62, 6.55]	207/257 (80.5%)	67/134 (50.0%)	–	–	–	
PILLAR	2.23 [1.07, 4.65]	62/77 (80.5%)	50/77 (64.9%)	–	–	–	
Pooled[e]	3.67 [2.69, 5.01] χ^2 = 2.18 (df: 2), p = 0.34, I^2 = 8%			–	–	–	
					TVR12+PR24/48		
ADVANCE	–	–	–	158/361 (43.8%)	271/363 (74.7%)	3.78 [2.76, 5.19]	
					BOC24+PR28/48		
SPRINT-2	–	–	–	132/363 (36.4%)	230/368 (62.6%)	2.92 [2.16, 3.95]	

SVR24 = sustained virological response at 24 weeks after the end of treatment; PR = peginterferon alfa and ribavirin; OR = odds ratio; CI = confidence interval; SMV = simeprevir; TVR = telaprevir; BOC = boceprevir

[a] SMV + PR vs placebo + PR. An OR >1 indicates treatment effect favouring SMV+PR i.e. improvement in odds of obtaining SVR24

[b] Placebo was given in addition to PR.

[c] TVR/BOC + PR vs placebo + PR. An OR >1 indicates treatment effect favouring TVR/BOC+PR i.e. improvement in odds of obtaining SVR24

[d] SMV + PR vs TVR/BOC + PR. An OR >1 indicates treatment effect favouring SMV+PR i.e. improvement in odds of obtaining SVR24

[e] Pooled using random effects model.

6.5 There were three trials investigating the treatment effect of simeprevir + PR relative to placebo + PR in treatment naïve patients. To enable presentation of a benefits and harms table, QUEST-1 was selected as the "representative" simeprevir trial to be included in the indirect comparisons, because among the three simeprevir trials, the SVR24 rate in the common reference arm of QUEST-1 was the closest to the SVR24 rates in the common reference arms in the telaprevir and boceprevir trials. It should be highlighted that the RDs from these indirect comparisons are only indicative, because:

- the trials might not be sufficiently exchangeable for a reliable estimate of the comparative effectiveness and safety of simeprevir + PR versus telaprevir/boceprevir + PR;
- absolute measures of comparative treatment effect (e.g. RD) vary with the baseline risk of the patient population in which the treatment is used; and
- the results of the indirect comparison of QUEST-1 with the boceprevir and telaprevir trials may be biased in favour of simeprevir in terms of SVR24, as the simeprevir-related increase in SVR24 reported in QUEST-1 was higher than the pooled result of the three simeprevir trials (30.3% vs 27.0%)

Summary of indicative comparative benefits and harms for simeprevir + PR versus telaprevir + PR or boceprevir + PR in treatment naïve patients – indirect comparison

Trial ID	SMV + PR vs placebo + PR			TVR/BOC + PR vs placebo + PR			Indirect comparison[b] RD % [95% CI]
	RD % [95% CI]	SMV12+ PR24/48 n/N (%)	PR48[a] n/N (%)	PR48[a] n/N (%)	Comparator n/N (%)	RD % [95% CI]	
Benefits							
Sustained virological response at 24 weeks after the end of treatment (MCID = -12%)							
QUEST-1	30.3% [20.4%, 40.2%]	210/264 (79.5%)	64/130 (49.2%)	–	–	–	
					TVR12+PR24/48		SMV+PR vs TVR+PR: -0.6% [-12.6%, 11.4%]
ADVANCE	–	–	–	158/361 (43.8%)	271/363 (74.7%)	30.9% [24.1%, 37.7%]	
					BOC24+PR28/48		
SPRINT-2	–	–	–	132/363 (36.4%)	230/368 (62.6%)	26.2% [19.2%, 33.2%]	SMV+PR vs BOC+PR: 4.2% [-7.9%, 16.3%]
Harms							
Serious adverse events							
QUEST-1	-2.4% [-7.1%, 2.4%]	10/264 (3.8%)	8/130 (6.2%)	–	–	–	
					TVR12+PR24/48		SMV+PR vs TVR+PR: -4.8% [-11.0%, 1.3%]
ADVANCE	–	–	–	24/361 (6.6%)	33/363 (9.1%)	2.4% [-1.5%, 6.4%]	
					BOC24+PR28/48		
SPRINT-2	–	–	–	31/363 (8.5%)	42/368 (11.4%)	2.9% [-1.5%, 7.2%]	SMV+PR vs BOC+PR: -5.2% [-11.7%, 1.2%]
Adverse events leading to treatment discontinuation							
QUEST-1	-5.5% [-11.2%, 0.3%]	12/264 (4.5%)	13/130 (10.0%)	–	–	–	
					TVR12+PR24/48		SMV+PR vs TVR+PR: -8.2% [-15.2%, -1.1%]
ADVANCE	–	–	–	26/361 (7.2%)	36/363 (9.9%)	2.7% [-1.4%, 6.8%]	
					BOC24+PR28/48		
SPRINT-2	–	–	–	57/363 (15.7%)	45/368 (12.2%)	-3.5% [-8.5%, 1.5%]	SMV+PR vs BOC+PR: -2.0% [-9.6%, 5.6%]
Anaemia							
QUEST-1	-2.2% [-10.2%, 5.8%]	43/264 (16.3%)	24/130 (18.5%)	–	–	–	
					TVR12+PR24/48		SMV+PR vs TVR+PR: -20.0% [-30.3%, -9.7%]
ADVANCE	–	–	–	70/361 (19.4%)	135/363 (37.2%)	17.8% [11.4%, 24.2%]	
					BOC24+PR28/48		

SPRINT-2	–	–	–	107/363 (29.5%)	182/368 (49.5%)	20.0% [13.0%, 26.9%]	SMV+PR vs BOC+PR: -22.2% [-32.8%, -11.6%]

PR = peginterferon alfa and ribavirin; RD = risk difference; CI = confidence interval; SMV = simeprevir; MCID = minimal clinically important difference specified as the non-inferiority margin in the submission; TVR = telaprevir; BOC = boceprevir

[a] Placebo was given in addition to PR.

[b] RDs from the indirect comparisons were calculated during the evaluation

[redacted]

6.6 TREATMENT EXPERIENCED – HEAD-TO-HEAD TRIAL:

The ESC considered that the direct comparison of SMV and TEL in the ATTAIN trial was the most informative evidence for supporting the claim of non-inferior efficacy.

[redacted]

6.7 TREATMENT EXPERIENCED – INDIRECT COMPARISON:

Due to the known varying virological response among prior relapsers, prior partial responders and prior null responders, the SVR24 results are presented according to prior response subgroups. The safety results, however, are summarised across the whole treatment experienced population, as safety is not expected to differ among the three subgroups. The following table does not include the benefits of simeprevir versus telaprevir in prior partial or null responders and the harms of simeprevir versus telaprevir in treatment experienced patients, due to the availability of the direct evidence. The submission does not present evidence comparing the effectiveness of simeprevir + PR over boceprevir + PR in prior null responders. One simeprevir trial (ASPIRE) and one boceprevir trial (Trial 5685) are not included in the table below, as the PI-recommended response-guided therapy (RGT) was not used in one subgroup

(prior relapsers) in ASPIRE and in all Trial 5685 subjects (prior relapsers and partial responders)

Summary of indicative comparative benefits and harms for simeprevir + PR versus telaprevir + PR or boceprevir + PR in treatment experienced patients – indirect comparison

Trial ID	SMV + PR vs placebo + PR			TVR/BOC + PR vs placebo + PR			Indirect comparison RD [95% CI][b]
	RD [95% CI]	SMV12+PR24/48 n/N (%)	PR48[a] n/N (%)	PR48[a] n/N (%)	Comparator n/N (%)	RD [95% CI]	
Benefits[c]							
Sustained virological response at 24 weeks after the end of treatment – prior relapsers (MCID = -12%)							
PROMISE	43.5% [34.0%, 53.0%]	201/260 (77.3%)	45/133 (33.8%)	–	–	–	
					TVR12+PR24/48		SMV+PR vs TVR+PR: -16.4% [-31.6%, -1.3%]
REALIZE	–	–	–	16/68 (23.5%)	121/145 (83.4%)	59.9% [48.2%, 71.7%]	
					BOC32+PR36/48		
RESPOND-2	–	–	–	15/51 (29.4%)	72/105 (68.6%)	39.2% [23.8%, 54.5%]	SMV+PR vs BOC+PR: 4.3% [-13.7%, 22.4%]
Sustained virological response at 24 weeks after the end of treatment – prior partial responders (MCID = -12%)							
ASPIRE	56.5% [33.9%, 79.1%]	15/23 (65.2%)	2/23 (8.7%)	–	–	–	
					BOC32+PR36/48		SMV+PR vs BOC+PR 23.1% [-4.5%, 50.6%]
RESPOND-2	–	–	–	2/29 (6.9%)	23/57 (40.4%)	33.5% [17.7%, 49.2%]	
Harm[c]							
Serious adverse events – all treatment experienced patients							
PROMISE	-2.9% [-8.3%, 2.5%]	14/260 (5.4%)	11/133 (8.3%)	–	–	–	
					BOC32+PR36/48		SMV+PR vs BOC+PR: -10.0% [-18.0%, -1.9%]
RESPOND-2	–	–	–	4/80 (5.0%)	39/323 (12.1%)	7.1% [1.1, 13.0%]	
Adverse events leading to treatment discontinuation – all treatment experienced patients							
PROMISE	-3.0% [-7.2%, 1.3%]	6/260 (2.3%)	7/133 (5.3%)	–	–	–	
					BOC32+PR36/48		SMV+PR vs BOC+PR: -10.7% [-17.0%, -4.3%]
RESPOND-2	–	–	–	2/80 (2.5%)	33/323 (10.2%)	7.7% [3.0%, 12.5%]	
Anaemia – all treatment experienced patients							
PROMISE	-2.7% [-10.5%, 5.2%]	40/260 (15.4%)	24/133 (18.0%)	–	–	–	
					BOC32+PR36/48		SMV+PR vs BOC+PR: -27.2% [-40.2%, -14.3%]
RESPOND-2	–	–	–	16/80 (20.0%)	144/323 (44.6%)	24.6% [14.3%,	

						34.9%]	

PR = peginterferon alfa and ribavirin; RD = risk difference; CI = confidence interval; SMV = simeprevir; MCID = minimal clinically important difference specified as the non-inferiority margin in the submission; TVR = telaprevir; BOC = boceprevir

[a] Placebo was given in addition to PR.

[b] RDs from the indirect comparison were calculated during the evaluation

[c] For the comparative safety of simeprevir+PR vs telaprevir+PR in treatment experienced patients and comparative effectiveness of simeprevir + PR vs telaprevir + PR in prior null or partial responders

[redacted]

6.8 The ESC noted the statistically inferior SVR24 observed among prior relapsers who received SMV + PR compared with TVR + PR. The ESC considered that the importance of this result was low given the limitations of the indirect comparison, the similarity in the absolute SVR24 observed among SMV + PR and TVR + PR recipients (77.3% vs 83.4%), and the relatively small number of prior relapsers among all NS3/4A eligible patients. Overall, on the basis of the head to head trials and supported by indirection comparisons, SMV appears to have the same effect as TEL/BOC in the treatment of HCV Genotype 1 in treatment naïve and treatment-experienced patients.

6.9 The PBAC noted that on the basis of indirect evidence presented by the submission, for every 100 treatment naïve patients treated with SMV12+PR24/48 in comparison to TVR12+PR24/48 or BOC24+PR28/48:

- SMV appears to be no worse than TEL/BOC in the treatment of HCV Genotype 1
- Approximately 5 fewer patients would have SAEs during the treatment period
- Approximately 2-8 fewer patients would have treatment discontinuations due to AEs during the treatment period
- Approximately 20-22 fewer patients would have anaemia during the treatment period

The PBAC agreed with the ESC who considered that similar comparative benefits and harms would be realised in the treatment experienced patients

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

Clinical claim

6.10 The submission describes simeprevir + PR as non-inferior in terms of comparative effectiveness and superior in terms of comparative safety versus telaprevir + PR or boceprevir + PR for the treatment of HCV genotype 1 infection

	Non-inferior effectiveness claim				Superior safety claim
	Treatment naïve	Prior relapsers	Prior partial responders	Prior null responders	All patients
Simeprevir + PR vs telaprevir + PR	The ESC considered that claim is weakly supported, given: 1) the poor exchangeability of trials involved in the indirect comparison; and 2) the CI including reductions in	Not supported, given the statistically inferior treatment effect of simeprevir + PR vs telaprevir + PR from the indirect comparison.	The ESC considered the claim appears reasonable based on the SVR12 results from ATTAIN.	The ESC considered the claim is weakly supported, as the pre-specified subgroup analysis in ATTAIN does not exclude reductions in SVR12 rates which could be clinically important to this	The ESC considered the claim appears well supported, based on consistent findings from direct and indirect evidence, notwithstandin

	SVR24 rates which could be clinically relevant			population	g the variability in results of the indirect comparisons which were limited by the poor exchangeabilit y of trials, with respect to predictors of response to interferon-based therapy.
Simeprevir + PR vs boceprevir + PR	The ESC considered the claim appears reasonable, although the indirect comparison is limited by the poor exchangeability of trials involved	The ESC considered the claim is weakly supported, given the poor trial exchangeability and the CI including reduction in SVR24 rates which could be clinically relevant	The ESC considered the claim appears reasonable, although the indirect comparison is limited by the poor exchangeability of trials involved	The ESC considered the claim not supported as no clinical evidence provided	

PR = peginterferon and ribavirin; CI = confidence interval; PI = product information; SVR = sustained virological response
Source: Table compiled during the evaluation

6.11 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.

6.12 The PBAC considered that the claim of superior comparative safety was reasonable.

Economic analysis

6.13 The submission presents a cost-minimisation analysis compared to telaprevir, with simeprevir 150mg once daily being equi-effective to telaprevir 750mg three times per day. The dispensed price per maximum quantity (DPMQ) of simeprevir is proposed to be the same as that of telaprevir, (weighted based on the proportion of patients in public and private settings) per prescription for 6 weeks of simeprevir treatment. The proposed dose relativity does not consider the differences in treatment durations that are dependent on a patient's virologic response. Nevertheless, given that the standard treatment duration of simeprevir plus PR is similar to that of telaprevir plus PR, the proposed dose relativity of simeprevir to telaprevir appears reasonable.

6.14 The DPMQ of simeprevir is proposed to be the same as that of the main comparator telaprevir, [redacted] (weighted DPMQ based on the proportion of patients in public and private settings) per prescription for 6 weeks of simeprevir treatment. [redacted]

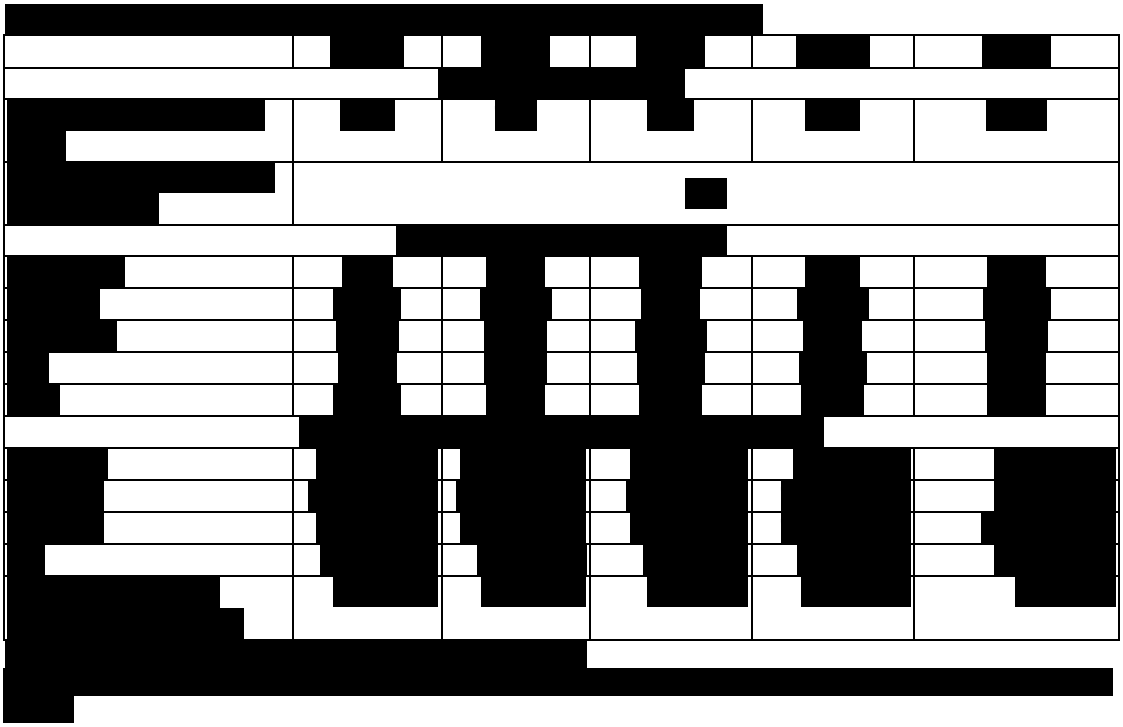
[redacted]

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

Estimated PBS usage & financial implications

6.15 The submission assumes that simeprevir will not contribute to the growth of the DAA market for HCV, but that simeprevir will substitute equally for its pharmacological analogues, telaprevir and boceprevir. The submission estimates DAA script numbers and patient numbers based on the Medicare PBS data for telaprevir and boceprevir from 2013. The current estimated market share of telaprevir and boceprevir is 53%

and 47% respectively. The submission expects that simeprevir will have a market uptake rate of [redacted] Given the superior safety profile for simeprevir over telaprevir and boceprevir, the lower pill burden and that patients may be waiting for alternate treatment options with fewer side effects, the ESC considered that assumption that simeprevir would not contribute to market growth may not be correct and the market for NS3/4A protease inhibitors may increase.



6.16 The submission's estimate of cost savings to the PBS is related to the reduction in use of other DAA drugs, telaprevir and boceprevir, and concomitant therapy with PR (peginterferon + ribavirin) due to the differences in RGT criteria and virologic stopping rules among these DAAs. The cost savings presented in the financial estimates of the submission are uncertain given the estimated number of prescriptions per patient for each treatment are based on virologic response from single treatment arms across different trials and the comparability of the populations achieving these virologic responses is unknown. The submission anticipates that listing simeprevir on the PBS will have no impact on MBS.

6.17 The ESC considered that cost savings through reduced use of PR and a superior safety profile, are likely to be realised but the magnitude was uncertain as:

- the listing of simeprevir, with fewer side effects as telaprevir/boceprevir, may increase the market of NS3/4A protease inhibitors;
- the potential listing of other treatments could have implications for the market share of the NS3/4A inhibitor class of HCV drugs.

6.18 The sponsor state that they would be willing to join the Deed of Agreement that currently exists in relation to the supply of direct anti-viral medicines and be subject to the requirement and obligations that it sets out. The PBAC agreed that simeprevir should join into the same risk share agreement as telaprevir and boceprevir.

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

7 PBAC Outcome

7.1 The PBAC recommended the Section 100 (Highly Specialised Drugs Program) listing of simeprevir, in combination with PR, to treat hepatitis C virus (HCV) genotype 1 infection in treatment naïve and treatment experienced patients who meet certain criteria, with a maximum quantity of 6 packs with 0 repeats. The listing is on the basis of non-inferiority to telaprevir and boceprevir. The equi-effective doses are simeprevir 150mg once daily being equi-effective to telaprevir 750mg three times per day.

7.2 The PBAC considered that telaprevir and boceprevir were appropriate comparators on the basis that they are pharmacological analogues, and are the therapies most likely to be replaced in Australia at the time of consideration of the submission. However, the PBAC noted that the likely treatment algorithm for HCV is changing rapidly, particularly with the development of interferon-free regimens. As an example of the rapidly evolving treatment landscape, both telaprevir and boceprevir are now not recommended for the treatment of patients with HCV genotype 1 in the guidelines of the AASLD and the Infectious Disease Society of America. The PBAC noted that over 30 DAAs are in clinical development, including inhibitors of NS5A, NS5B and NS3/4A as well as host-targeting antivirals.

7.3 The PBAC agreed with the ESC that patients with HCV Genotype 1 may not be immediately seeking treatment to avoid the adverse side effect profile of telaprevir and boceprevir or are waiting for short course and/or IFN-free treatments. With the listing of simeprevir, some patients may opt to be treated with simeprevir given the reduced side effect profile compared to other NS3/4A inhibitors. Considering the likely larger patient population who would prefer to wait for IFN-free treatment options (which may include simeprevir), a peginterferon-associated comparator may be inappropriate. In this context, the PBAC considered that the long term validity of the cost-minimisation analysis was uncertain and should be reviewed as other hepatitis C treatments become available.

7.4 In addition to the trial evidence provided in the submission, the PBAC noted the sponsor's addendum providing the SVR24 data of the ATTAIN trial [redacted], which was provided after the ESC meeting, which showed similar SVR as observed at week 12.

7.5 The PBAC considered that the submission supported the claim that simeprevir is non-inferior in terms of comparative effectiveness (in achieving an SVR) and superior in terms of safety when compared with boceprevir and telaprevir. The PBAC considered that a cost-minimisation analysis was the appropriate approach at present, but as the likely treatment algorithm for HCV is changing rapidly, this approach of valuing the comparative efficacy of simeprevir may require early review.

7.6 The PBAC agreed with ESC that cost savings would likely be realised through reduced use of PR and a superior safety profile but the magnitude of the savings was uncertain.

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

7.8 The PBAC noted that, with the listing of simeprevir, that there are flow-on implications to the PBS-listings of other medicines, which may take time to finalise in consultation with affected sponsors.

7.9 The PBAC recommended that simeprevir is not suitable for prescribing by nurse practitioners as it is a Section 100 medicine.

7.10 The PBAC recommended that the Safety Net 20 Day Rule should not apply to simeprevir, as it does not apply to items supplied under Section 100.

7.11 Advice to the Minister under Section 101 3BA of the National Health Act:
The PBAC advised the Minister that under Section 101 3BA of the National Health Act, simeprevir should be treated as interchangeable on an individual patient basis with boceprevir and telaprevir.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty (packs)	№.of Rpts	Proprietary Name and Manufacturer
SIMEPREVIR simeprevir sodium 150 mg capsule, 7	6	0	Olysio® JC

Treatment naïve patients:

Category/Program	Section 100 (Highly Specialised Drugs Program)
Episodicity:	
Severity:	
Condition:	Chronic genotype 1 hepatitis C infection
Indication:	Chronic genotype 1 hepatitis C infection
Restriction:	Public Hospital Authority Required (Streamlined) Private Hospital Authority Required
Treatment criteria:	Must be treated in an accredited treatment centre

Clinical criteria:	Patient must have compensated liver disease AND Patient must not have received prior treatment with interferon alfa or peginterferon alfa for hepatitis C AND The treatment must be in combination with peginterferon alfa and ribavirin AND The treatment with simeprevir must be limited to a maximum duration of 12 weeks AND The treatment must cease if the results of an HCV RNA quantitative assay at week 4 show that the plasma HCV RNA is 25 IU/mL or greater
Population criteria:	Patient must be 18 years or older AND Patient must not be pregnant or breastfeeding. Female partners of male patients must not be pregnant. Patients and their partners must each be using an effective form of contraception if of child-bearing age
Prescriber instructions:	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. Patients who have received prior treatment with an NS3/4A protease inhibitor are not eligible to receive PBS-subsidised simeprevir, except where the patient has developed an intolerance to the other NS3/4A protease inhibitor of a severity necessitating permanent treatment withdrawal. Details of the intolerance must be documented in the patient's medical records.
Administrative Advice	Note No increase in the maximum quantity or number of units may be authorised Note No increase in the maximum number of repeats may be authorised Note 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 education/counsellor for patients; and (b) 24-hour access by patients to medical advice; and (c) an established liver clinic

Treatment experienced patients:

Condition:	Chronic genotype 1 hepatitis C infection
Restriction:	Section 100 (Highly Specialised Drugs Program) Public Hospital -Authority Required (Streamlined) Private Hospital-Authority Required
Treatment criteria:	Must be treated in an accredited treatment centre

Clinical criteria:	Patient must have compensated liver disease, AND Patient must have received prior treatment with interferon alfa or peginterferon alfa for hepatitis C, AND The treatment must be in combination with peginterferon alfa and ribavirin, AND The treatment with simeprevir must be limited to a maximum duration of 12 weeks, AND The treatment must cease if the results of an HCV RNA quantitative assay at week 4 show that the plasma HCV RNA is 25 IU/mL or greater
Population criteria:	Patient must be 18 years or older, AND Patient must not be pregnant or breastfeeding. Female partners of male patients must not be pregnant. Patients and their partners must each be using an effective form of contraception if of child-bearing age.
Prescriber instructions	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. Patients who have received prior treatment with an NS3/4A protease inhibitor are not eligible to receive PBS-subsidised simeprevir, except where the patient has developed an intolerance to the other NS3/4A protease inhibitor of a severity necessitating permanent treatment withdrawal. Details of the intolerance must be documented in the patient's medical records.
Administrative Advice	Note No increase in the maximum quantity or number of units may be authorised. Note No increase in the maximum number of repeats may be authorised. Note 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.

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

Janssen is pleased that patients will soon be able to access Simeprevir under the PBS.