

5.05 GLECAPREVIR with PIBRENTASVIR, Tablet containing 100 mg glecaprevir with 40 mg pibrentasvir, Maviret[®], AbbVie Pty Ltd.

1 Purpose of Application

- 1.1 The submission requested General Schedule and Section 100 (Highly Specialised Drugs Program) Authority Required (STREAMLINED) listings for the fixed dose combination (FDC) of glecaprevir and pibrentasvir (GLE-PIB) for the treatment of chronic hepatitis C (CHC) for genotypes 1-6.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with chronic hepatitis C (CHC), genotypes 1-6, including those who have failed prior treatment with an NS5A inhibitor.
Intervention	100 mg glecaprevir with 40 mg pibrentasvir (GLE-PIB) tablets, 3 tablets taken once daily. Treatment duration depends on genotype, cirrhotic status and prior treatment experiences (refer to Table 2).
Comparator	A fixed dose combination of sofosbuvir 400mg and velpatasvir 100mg (SOF-VEL), once daily, for 12 weeks, a pangenotypic regimen for the treatment of genotypes 1-6 CHC, in NS5A inhibitor naïve patients. In NS5A experienced patients, 'no treatment' may be an appropriate comparator.
Outcomes	Sustained virologic response at 12 weeks post treatment (SVR12) and rates of adverse events
Clinical claim	The submission claimed that GLE-PIB is non-inferior to SOF-VEL based on an informal comparison of single-arm studies.

Source: compiled during the evaluation

2 Requested listing

- 2.1 To be finalised. The submission's proposed restriction is given below.
- 2.2 The restriction requests an authority required (streamlined) listing, whereas the current PBS listings for the DAA for HCV infection are authority required (telephone). The PBAC recommended an authority required (telephone) listing for sofosbuvir with velpatasvir in November 2016. Additionally, the different durations of treatment necessary for GLE-PIB in different settings (see Table 2) may make a telephone authority appropriate to ensure that the special pricing arrangement (SPA) requested by the sponsor can be properly administered (as is the case with the current DAA listings).
- 2.3 The pre-PBAC Response argued that any SPA would be administered via distinct PBS codes associated with each treatment duration and that as the SPA is structured in such a way that the same cost for treatment is applied per patient, no risk is posed to the administration of the SPA by an authority required (streamlined) listing. The sponsor also argued that the request for a streamlined listing supports the simplification of treatment decisions and prescribing to support the management of HCV treatment to all people in Australia – noting that all oral DAA therapies are considered safe and well tolerated; they are not restricted by patient population;

Public Summary Document - July 2017 PBAC meeting

and are pan-genotypic, eliminating the risk of prescribing to inappropriate patient populations.

Name, Restriction, Manner of administration and form	Max qty packs	Max qty units	No. of Rpts	Dispensed Price for Max. Qty*	Proprietary Name and Manufacturer
GLECAPREVIR/PIBRENTASVIR Tablet 100 mg/40 mg, 84	1	84	3	S100 Public: \$ [REDACTED] S100 Private: \$ [REDACTED] S85 General: \$ [REDACTED]	To be determined AbbVie Pty Ltd

*The submission acknowledged that currently listed direct acting antivirals have special pricing arrangements and requested an effective price to match that of sofosbuvir/velpatasvir.

Category/ Program	General Schedule and S100 highly specialised drug program (Public and Private)
Prescriber type	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	N/A
Severity:	Chronic
Condition:	HCV infection
PBS Indication:	Chronic HCV infection
Treatment phase:	Initial
Restriction:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Treatment criteria:	Must be treated by a medical practitioner experienced in the treatment of chronic hepatitis C infection; or in consultation with a gastroenterologist, hepatologist or infectious diseases physician experienced in the treatment of chronic hepatitis C infection.
Clinical criteria:	Patient must meet the criteria set out in the General Statement for Drugs for the Treatment of Hepatitis C; AND Patient must be taking this drug as part of a regimen set out in the matrix in the General Statement for Drugs for the Treatment of Hepatitis C, based on the hepatitis C virus genotype, patient treatment history and cirrhotic status; AND The treatment must be limited to a maximum duration of 16 weeks.
Population criteria:	Patient must be aged 18 years or older.

2.4 The submission was based on a cost-minimisation analysis of glecaprevir/pibrentasvir in comparison with a FDC of sofosbuvir and velpatasvir. The submission acknowledged that all reimbursed oral direct acting antivirals (DAA) regimens have special pricing arrangements but the specific arrangement for sofosbuvir/velpatasvir is not known. The sponsor indicated a willingness to accept the sofosbuvir/velpatasvir effective price on the basis of a cost-minimisation analysis.

2.5 Glecaprevir/pibrentasvir is an FDC oral tablet containing 100 mg glecaprevir and 40 mg pibrentasvir. The recommended dose of glecaprevir/pibrentasvir is three tablets taken once daily in the morning with food. The proposed duration of

treatment differs across proposed patient populations from 8 weeks to 16 weeks and is summarised in the table below. The ESC noted that the final durations of treatment recommended for use in each subgroup will depend upon the outcomes of the TGA evaluation.

- 2.6 In its pre-PBAC response the sponsor requested that the subgroup of patients with prior NS5A inhibitor treatment experience be removed from consideration in the current submission. The PBAC acknowledged this request and did not consider this patient subgroup in its deliberations.

Table 2: Proposed duration of treatment with glecaprevir/pibrentasvir in specific patient subgroups

Patient population	Duration
Treatment naïve	
Genotype 1-6 without cirrhosis	8 weeks (1 repeat)
Genotype 1-6 with cirrhosis	12 weeks (2 repeats)
Treatment experienced (no prior NS5A inhibitor)	
Genotype 1-2 and 4-6 without cirrhosis	8 weeks (1 repeat)
Genotype 1-2 and 4-6 with cirrhosis	12 weeks (2 repeats)
Genotype 3 with or without cirrhosis	16 weeks (3 repeats)
Treatment experienced with prior NS5A inhibitor	
Genotype 1-6 with or without cirrhosis	16 weeks (3 repeats)

NS5A = non-structural protein 5A.

Treatment experienced (no prior NS5A inhibitor) refers to prior treatment with peg-interferon, ribavirin, protease inhibitors and/or sofosbuvir. Treatment experienced with prior NS5A inhibitor refers to prior treatment with sofosbuvir + ledipasvir, daclatasvir + sofosbuvir, daclatasvir + pegIFN and ribavirin, paritaprevir/ritonavir + ombitasvir + dasabuvir, daclatasvir + asunaprevir.

Source: Table A-2, p29 of the submission.

- 2.7 Glecaprevir/pibrentasvir is not indicated for patients with decompensated cirrhosis.
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. At the time of PBAC consideration, no TGA documents were available. The sponsor's Pre PBAC response stated at the time of the July PBAC meeting glecaprevir/pibrentasvir remained under evaluation by the TGA.
- 3.2 This was the first submission requesting PBS-listing of glecaprevir/pibrentasvir FDC.
- 3.3 The pre-PBAC response noted that glecaprevir/pibrentasvir has recently received regulatory approval in the European Union and is anticipating regulatory approval in the United States shortly. It stated that based on the EU and FDA regulatory assessments, it is expected that the TGA proposed indication and dosage regimens for NS5A naïve patients will remain as presented in the submission.

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

4 Population and disease

- 4.1 Hepatitis C is a blood-borne inflammatory liver disease caused by hepatitis C virus (HCV), with around 75-80% of people exposed to HCV developing chronic infection which may lead to cirrhosis, liver failure, hepatocellular carcinoma and death. Approximately 230,000 people in Australia were estimated to be living with chronic HCV infection in 2014 (Kirby 2015).
- 4.2 The glecaprevir/pibrentasvir FDC is an alternative treatment option to hepatitis C antivirals already listed on the PBS for the treatment of this condition. Glecaprevir is a HCV NS3/4A protease inhibitor. HCV NS3/4A protease is necessary for the creation of proteins essential for viral replication. Pibrentasvir is a HCV NS5A protein inhibitor. HCV NS5A protein is essential for viral RNA replication and virion assembly.

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

5 Comparator

- 5.1 The submission nominated sofosbuvir/velpatasvir as the main comparator. This is the appropriate comparator for the majority of patients. Sofosbuvir/velpatasvir was recommended by the PBAC in November 2016 for the treatment of CHC genotypes 1-6. This listing has not yet taken effect. The ESC considered that the other currently listed DAA based regimens may also be appropriate comparators in patients who have not failed prior NS5A inhibitors.
- 5.2 Sofosbuvir/velpatasvir may not be an appropriate comparator for patients who have failed prior NS5A inhibitors. Although the current PBS restrictions for DAAs do not preclude the use of sofosbuvir/velpatasvir, or an alternative DAA regimen, in patients who have previously failed treatment with an NS5A inhibitor, sofosbuvir/velpatasvir for 12 weeks is unlikely to be suitable for patients who have failed treatment with an NS5A inhibitor since no trials of 12 weeks of sofosbuvir/velpatasvir included patients who had previously failed an NS5A inhibitor. There are no regimens listed or recommended on the PBS that have been recommended by the evidence based guidelines of the European Association for the Study of the Liver (EASL) for this patient group. Therefore, no treatment may be a more appropriate comparator for this population. The PSCR (p4) acknowledged that for some patients previously treated with an NS5A inhibitor, no treatment may be the appropriate comparator.
- 5.3 The ESC considered the appropriate comparator for patients previously treated with an NS5A inhibitor should be no treatment. The pre-PBAC response agreed that for some patients previously treated with a NS5A inhibitor, no treatment may be the appropriate comparator. However, as noted above (paragraph 2.6), the sponsor requested that this patient group be removed from consideration in the current submission, noting that the clinical and economic issues raised relevant to this group of patients will be addressed in a subsequent minor submission to the PBAC.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician presented an overview on the progress of HCV elimination and discussed barriers to general practitioner (GP) prescribing including: the complexity of treatment regimes, HCV genotype differences and clinician experiences with the use of the current PBS telephone authority restriction. The presentation included information on HCV-related cirrhosis and the treatment challenges for clinicians in this population. The PBAC considered that the hearing was informative as it provided a clinical perspective on the complexities in treating HCV, particularly in relation to general practitioners.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (2) and organisations (14) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with glecaprevir/pibrentasvir including: the addition of another pan-genotypic treatment choice for patients with HCV - which is valuable for prescribers and in preventing relapse and resistant strains emerging; the short duration of treatment and high cure rates across all genotypes - including the hard-to-treat genotype 3; and that it appears to be efficacious for people with severe chronic kidney disease, compensated cirrhosis, and prior antiviral treatment experience.

6.3 The PBAC noted the advice received from a variety of community and professional organisations representing people living with hepatitis. The PBAC specifically noted the advice that the simplified prescribing associated with a pan-genotypic DAA will encourage the involvement of GPs. The PBAC noted that this advice was supportive of the evidence provided in the submission.

Clinical trials

6.4 The submission was based on an unadjusted comparison (without a common reference) of seven studies of glecaprevir/pibrentasvir and five studies of sofosbuvir/velpatasvir.

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

Public Summary Document - July 2017 PBAC meeting

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
GLECAPREVIR/PIBRENTASVIR TRIALS FOR COMPARISON OF SINGLE-ARM STUDIES		
ENDURANCE-1 (M13-590)	Internal study report: Trial report M13-590. A Randomised, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Adults with Chronic Hepatitis C Virus Genotype 1 Infection (ENDURANCE-1)	Date of report: 11/11/2016
	Zeuzem et al. (2016) ENDURANCE-1: Efficacy and Safety of 8-versus 12-week Treatment with ABT-493 / ABT-530 in patients with Chronic HCV Genotype 1 Infection.	Hepatology official journal of the American Association for the Study of Liver Diseases. 2016, Vol.63(1), p.132A
EXPEDITION-1 (M14-172)	Internal study report: Trial report M14-172. A Single Arm, Open-Label Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Adults with Chronic Hepatitis C Virus Genotype 1, 2, 4, 5 or 6 Infection and Compensated Cirrhosis	Date of report: 2/12/2016
ENDURANCE-3 (M13-594)	Internal study report: Trial report M13-594. A Randomised, Open-Label, Active-Controlled, Multicenter Study to Compare Efficacy and Safety of ABT-493/ABT-530 to Sofosbuvir Co-Administered With Daclatasvir in Adults With Chronic Hepatitis C Virus Genotype 3 Infection (ENDURANCE-3)	Date of report: 2/12/2016
	Foster et al (2016) A Phase 3, Randomised, Open-Label, Active-Controlled Study to Compare Efficacy and Safety of ABT-493/ABT-530 to Sofosbuvir Co-Administered with Daclatasvir in Adults with HCV Genotype 3 Infection	Journal of Hepatology. 2016. Vol.64(2), pp.S292-S292
EXPEDITION-4 (M15-462)	Internal study report: Trial Report M15-462. A Single-Arm, Open-Label, Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Renally-Impaired Adults with Chronic Hepatitis C Virus Genotype 1 – 6 Infection	Date of report: 23/11/2016
SURVEYOR-I (M14-867)	Internal study report: Trial report M14-867. An Open-Label, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Co-Administration of ABT-493 and ABT-530 With and Without Ribavirin in Subjects With Chronic Hepatitis C Virus (HCV) Genotype 1, 4, 5, and 6 Infection (SURVEYOR-I)	Date of report: 20/5/2016
	Gane et al (2016) High Efficacy of ABT-493 and ABT-530 Treatment in Patients With HCV Genotype 1 or 3 Infection and Compensated Cirrhosis.	Gastroenterology. 2016. Vol.151(4), p.651
SURVEYOR-II (M14-868)	Internal study report: Trial report M14-868. A Randomised, Open-Label, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Co-Administration of ABT-493 and ABT-530 With and Without RBV in Subjects With Chronic Hepatitis C Virus (HCV) Genotypes 2, 3, 4, 5 or 6 Infection (SURVEYOR-II)	Date of report: 2/12/2016
	Gane et al (2016) High Efficacy of ABT-493 and ABT-530 Treatment in Patients With HCV Genotype 1 or 3 Infection and Compensated Cirrhosis.	Gastroenterology, 2016, Vol.151(4), p.651
	Wyles et al (2016) SURVEYOR-II, part 3: Efficacy and safety of ABT-493 / ABT-530 in patients with hepatitis C virus genotype 3 infection with prior treatment experience and/or cirrhosis.	Hepatology official journal of the American Association for the Study of Liver Diseases. 2016. Vol.63(1), p.62A
MAGELLAN-1 (M15-410)	Internal study report: Trial report M15-410. A Randomised, Open-Label, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Co-Administration	Date of report: 30/11/2016

Public Summary Document - July 2017 PBAC meeting

Trial ID	Protocol title/ Publication title	Publication citation
	of ABT-493 and ABT-530 (or ABT-493/ABT-530) With and Without Ribavirin in Adults With Chronic Hepatitis C Virus (HCV) Infection Who Failed a Prior Direct-Acting Antiviral Agent (DAA)-Containing Therapy	
SOFOSBUVIR-VELPATASVIR TRIALS FOR COMPARISONS OF SINGLE-ARM STUDIES		
ASTRAL-1 Fled et al (2015)	Feld et al (2015) Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection.	N Engl J Med 2015;373:2599-607.
	Feld et al (2015) A Phase 3 Double-Blind Placebo-Controlled Evaluation of Sofosbuvir/Velpatasvir Fixed Dose Combination for 12 Weeks in Naive and Experienced Genotype 1, 2, 4, 5, 6 HCV Infected Patients with and without Cirrhosis: Results of the ASTRAL-1 Study.	J Hepatol 2015;62(6) Suppl:1379A-1380A.
	Asselah et al (2015) The ASTRAL Studies: Evaluation of SOF/GS-5816 Single Tablet Regimen for the Treatment of Genotype 1-6 HCV Infection [Poster P1332].	J Hepatol 2015;62:S855-S6.
ASTRAL-2 Foster et al (2015)	Foster et al (2015) Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection	N Engl J Med 2015; 373:2608-2617
	Sulkowski et al (2015) A Randomised Controlled Trial of Sofosbuvir/GS-5816 Fixed Dose Combination for 12 Weeks Compared to Sofosbuvir with Ribavirin for 12 Weeks in Genotype 2 HCV Infected Patients: The Phase 3 ASTRAL-2 Study [Oral 205]	Hepatology 2015; 62: 1 (SUPPL) 313A.
	Asselah et al (2015) The ASTRAL Studies: Evaluation of SOF/GS-5816 Single Tablet Regimen for the Treatment of Genotype 1-6 HCV Infection [Poster P1332].	J Hepatol 2015;62:S855-S6.
ASTRAL-3 Foster et al (2015)	Foster et al (2015) Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection	N Engl J Med 2015; 373:2608-2617
	Asselah et al (2015) The ASTRAL Studies: Evaluation of SOF/GS-5816 Single Tablet Regimen for the Treatment of Genotype 1-6 HCV Infection [Poster P1332].	J Hepatol 2015;62:S855-S6.
	Mangia et al (2015) Sofosbuvir/GS-5816 Fixed Dose Combination for 12 Weeks Compared to Sofosbuvir with Ribavirin for 24 Weeks in Genotype 3 HCV Infected Patients: The Randomised Controlled Phase 3 ASTRAL-3 Study.	Hepatology 2015; 62: 1 (SUPPL) 338A.
Everson et al (2015)	Primary publication Everson GT, Townner WJ, Davis MN, Wyles DL, Nahass RG, Thuluvath PJ, Etkorn K, Hineostroza F, Tong M, Rabinovitz M, McNally J, Brainard DM, Han L, Doehle B, McHutchison JG, Morgan T, Chung RT, Tran TT. Sofosbuvir With Velpatasvir in Treatment-Naive Noncirrhotic Patients With Genotype 1 to 6 Hepatitis C Virus Infection: A Randomised Trial.	Ann Intern Med. 2015 Dec 1;163(11):818-26.
Pianko et al (2015)	Pianko S, Flamm SL, Shiffman ML, Kumar S, Strasser SI, Dore GJ, McNally J, Brainard DM, Han L, Doehle B, Mogalian E, McHutchison JG, Rabinovitz M, Townner WJ, Gane EJ, Stedman CA, Reddy KR, Roberts SK. Sofosbuvir Plus Velpatasvir Combination Therapy for Treatment-Experienced Patients With Genotype 1 or 3 Hepatitis C Virus Infection: A Randomised Trial.	Ann Intern Med. 2015 Dec 1;163(11):809-17.
	Pianko S, Flamm SL, Shiffman ML, Kumar S, Strasser SI, Dore GJ, et al. High Efficacy of Treatment with Sofosbuvir+GS-5816±Ribavirin for 12 Weeks in Treatment-Experienced Patients with Genotype 1 or 3 HCV Infection [Abstract 197].	American Association for the Study of Liver Diseases (AASLD); 2014 November 7-11; Boston MA United States.

Source: Table B-3, pp57-60 of the submission.

Public Summary Document - July 2017 PBAC meeting

- 6.6 ASTRAL-1, ASTRAL-2 and ASTRAL-3 were considered by the PBAC in November 2016 for the listing of sofosbuvir/velpatasvir.
- 6.7 ENDURANCE-1 specifically enrolled patients co-infected with HIV, who were naïve to antiretroviral therapy (ART) or who were on a stable ART regimen. The submission identified a trial of sofosbuvir/velpatasvir in patients with HIV (NCT02480712) yet excluded it due to a lack of results. The results of this trial were presented at The International Liver Congress in April 2016. Patients with GT1, 2, 3 and 4 with HIV received 12 weeks of SOF/VEL. Overall SVR12 was 95% http://www.natap.org/2016/EASL/EASL_32.htm - accessed 24/03/2017.
- 6.8 The key features of the studies for glecaprevir/pibrentasvir and sofosbuvir/velpatasvir are summarised in the table below.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population			Intervention	Key outcome
				HCV Gt ^d	Cirrhosis	Tx history		
Studies for glecaprevir/pibrentasvir								
EXPEDITION-1	146	SA, OL, MC 24 weeks	Low	1,2,4,5,6	Compensated cirrhosis	Tx naïve & experienced	GLE/PIB12	SVR12
EXPEDITION-4	104	SA, OL, MC 24 weeks	Low	1-6 Renally- impaired adults	Non-cirrhotic & compensated cirrhosis	Tx naïve & experienced	GLE/PIB12	SVR12
ENDURANCE-1	352	R, OL, MC 24 weeks	Low	1 (subgroup co-infected with HIV)	Non-cirrhotic	Tx naïve & experienced	GLE/PIB8	SVR12
ENDURANCE-3	157	R, OL, MC 24 weeks	Low	3	Non-cirrhotic	Tx naïve	GLE/PIB8	SVR12
SURVEYOR-I	34	R, OL, MC 24 weeks	Low	1	Non-cirrhotic	Tx naïve & experienced	GLE/PIB8	SVR12
SURVEYOR-II	55	R, OL, MC 24 weeks	Low	2	Non-cirrhotic	Tx naïve & experienced	GLE/PIB8	SVR12
	29			3	Non-cirrhotic	Tx naïve	GLE/PIB8	
	28			3	Compensated cirrhosis	Tx naïve & experienced	GLE/PIB12	
	40			3	Compensated cirrhosis	Tx Naïve	GLE/PIB12	
	22			3	Non-cirrhotic	Tx experienced	GLE/PIB16	
	48			3	Compensated cirrhosis	Tx experienced	GLE/PIB16	
	203			2, 4-6	Non-cirrhotic	Tx naïve & experienced	GLE/PIB8	
MAGELLAN-I	47	R, OL, MC 24 weeks	Low	1,4 ^a	Non-cirrhotic & compensated cirrhosis	Tx experienced (who failed a prior DAA)	GLE/PIB16	SVR12
Studies for sofosbuvir/velpatasvir								

Public Summary Document - July 2017 PBAC meeting

Trial	N	Design/ duration	Risk of bias	Patient population			Intervention	Key outcome
				HCV Gt ^d	Cirrhosis	Tx history		
ASTRAL-1	741 ^b	R, DB, MC 24 weeks (deferred Tx- OL CO for PBO arm)	Low	1, 2, 4, 5, 6 (all Gt 5 allocated to SOF/VEL12)	Non-cirrhotic & compensated cirrhosis	Tx naïve & experienced	SOF/VEL12 vs PBO12	SVR12
ASTRAL-2	269	R, OL, MC 24 weeks	Low	2	Non-cirrhotic & compensated cirrhosis	Tx naïve & experienced	SOF/VEL12 vs SOF+RBV12	SVR12
ASTRAL-3	558	R, OL, MC 24 or 36 weeks	High ^c	3	Non-cirrhotic & compensated cirrhosis	Tx naïve & experienced	SOF/VEL12 vs SOF+RBV24	SVR12
Everson (2015)	379	R, OL, MC 24 weeks	Low	1-6		Tx naïve	SOF/VEL12	SVR12
Pianko (2015)	323	R, OL, MC 24 weeks	Low	1,3		Tx experienced	SOF/VEL12	SVR12

SA = single-arm; DB = double-blind; Gt = genotype; HCV = hepatitis C virus; HIV = human immunodeficiency virus; MC = multi-centre; OL = open-label; R = randomised; PBO12 = placebo for 12 weeks; SOF+RBV12 = sofosbuvir plus ribavirin for 12 weeks; SOF+RBV24 = sofosbuvir plus ribavirin for 24 weeks; SOF/VEL12 = sofosbuvir/velpatasvir FDC for 12 weeks; GLE/PIB8 = glecaprevir/pibrentasvir FDC for 8 weeks; GLE/PIB12 = glecaprevir/pibrentasvir FDC for 12 weeks; GLE/PIB16 = glecaprevir/pibrentasvir FDC for 16 weeks; SVR12 = sustained virological response at 12 weeks following the completion of treatment; Tx = treatment.

Patients who discontinued (for whom there was no reported HCV RNA at 12 weeks following treatment) were classified as not achieving an SVR.

^a While the eligibility criteria permitted the enrolment of patients with GT1, 4, 5 or 6, in the relevant treatment arm (Arm E), 94% of patients were genotype 1 and 6% of patients were genotype 4.

^b Patients with HCV genotype 1, 2, 4, or 6 were randomly assigned in a 5:1 ratio to receive either SOF/VEL12 or placebo.

^c There was differential discontinuation between arms in ASTRAL-3, with more patients in the comparator arm (sofosbuvir plus ribavirin for 24 weeks) not starting (5 patients vs 1 patient) or discontinuing (21 vs 2 patients) study drug. While there was differential discontinuation in the ASTRAL-3 trial, the higher rates of discontinuation occurred in the sofosbuvir+ribavirin arm rather than the sofosbuvir/velpatasvir arm. Discontinuations were deemed to be failures when data were missing for SVR12. While this may have affected the comparative SVR12 rates in ASTRAL-3, it will not affect the comparison of sofosbuvir/velpatasvir versus glecaprevir/pibrentasvir that is relevant to the submission and clinical claim.

^d The reported genotypes represent those randomised into the relevant trial arms.

Source: constructed during the evaluation.

6.9 Patients in many of the glecaprevir/pibrentasvir studies were permitted to have failed regimens containing sofosbuvir, and patients in MAGELLAN-1 could have additionally failed an NS5A inhibitor, such as ledipasvir. No studies of sofosbuvir/velpatasvir included patients who had previously failed sofosbuvir or an NS5A inhibitor. Therefore, the efficacy of sofosbuvir/velpatasvir is largely unknown in this population.

6.10 EXPEDITION-4 specifically enrolled patients with renal impairment (eGFR<30mL/min/1.73m²). There are no sofosbuvir/velpatasvir studies with a similar population, and the safety and efficacy remains unknown in patients with severe renal impairment.

Comparative effectiveness

6.11 The results of SVR12 from relevant arms of individual studies for all genotypes are summarised in the table below.

Table 5: SVR12 for glecaprevir/pibrentasvir and sofosbuvir/velpatasvir in all genotypes (study arms relevant to the submission only)

Studies		SVR12	Pooled ^c
		n/N (%) [95% CI]	
Glecaprevir/pibrentasvir studies			
ENDURANCE-1		348/351 (99.1) [████████]	████████████████████
EXPEDITION-1		145/146 (99.3) [96.2, 100]	
ENDURANCE-3		149/157 (94.9) [90.2, 97.8]	
EXPEDITION-4		102/104 (98.1) [93.2, 99.8]	
SURVEYOR-I		████████████████████	
SURVEYOR-II	Arm J	53/54 (98.1) [████████]	
	Arm L ^a	28/29 (96.6) [82.2, 99.9]	
	Arm O	27/28 (96.4) [81.7, 99.9]	
	Arm Q1	39/40 (97.5) [86.8, 99.9]	
	Arm R1	21/22 (95.5) [77.2, 99.9]	
	Arm R2	45/47 (95.7) [85.5, 99.5]	
Arm S		196/203 (96.6) [93.0, 98.6]	
MAGELLAN-1 ^b		43/47 (91.5) [79.6, 97.6]	
Sofosbuvir/velpatasvir studies			
ASTRAL-1		618/624 (99.0) [97.9, 99.6]	1166/1192 (97.8) [96.8, 98.6]
ASTRAL-2		133/134 (99.3) [95.9, 100]	
ASTRAL-3		264/277 (95.3) [92.1, 97.5]	
Everson (2015)	Group 2	28/28 (100) [87.7, 100]	
	Group 4	25/27 (92.6) [75.7, 99.1]	
	Group 6	21/22 (95.5) [77.2, 99.9]	
Pianko (2015)	Group 3	27/27 (100) [87.2, 100]	
	Group 7	23/26 (88.5) [69.8, 97.6]	
	Group 11	27/27 (100) [87.2, 100]	

^aOnly treatment naïve patients included in this arm

^bIncluding patients who are treatment experienced to NS5A inhibitors

^cAs stated in Section B.5 of the commentary, the method of pooling used in the submission does not weight studies by variance. When SVR rates are pooled using a random effects meta-analysis of proportions (metaprop, Stata 14.1), with a Freeman-Tukey Double Arcsine Transformation to stabilise the variances, the results for the pooling for glecaprevir/pibrentasvir and sofosbuvir/velpatasvir are 97.7% [96.2%, 98.9%] and 98.3% [95.9%, 99.8%], respectively.

SVR12 = sustained virological response at 12 weeks following the completion of treatment

Source: Table B-23, p125 and Table B-24, p126 of the submission.

6.12 Across all included study arms for glecaprevir/pibrentasvir, SVR12 ranged from 91.5% in patients with genotypes 1, 4, 5 or 6 who were treatment experienced (including experienced to NS5A inhibitors) with or without cirrhosis (MAGELLAN-1) to 99.3% in patients with genotypes 1, 2, 4, 5 or 6, with cirrhosis who were either treatment naïve or treatment experienced (EXPEDITION-1). Pooling across all of these study results in a SVR12 of ██████████.

6.13 SVR12 rates were similar in the sofosbuvir/velpatasvir study arms, ranging from 88.5% in treatment experienced patients who were cirrhotic with genotype 3 HCV

(Pianko 2015) to 100% in three trial arms. The pooled results across all relevant sofosbuvir/velpatasvir study arms was 97.8% [95% CI 96.8, 98.6].

- 6.14 The pooled SVR rate in the glecaprevir/pibrentasvir study arms was similar to the pooled SVR rate in the sofosbuvir/velpatasvir study arms. This comparison may have been confounded by differences in patients enrolled into each of the trial arms with respect to HCV genotype, the presence or absence of cirrhosis, exposure to prior HCV treatments or other prognostic factors.
- 6.15 The submission also conducted a comparison of SVR12 from glecaprevir/pibrentasvir studies with those from the sofosbuvir/velpatasvir studies by genotype, the presence or absence of cirrhosis (for all genotypes and stratified by genotype) and exposure to prior treatments (for all genotypes and stratified by genotype). Overall, the comparison of glecaprevir/pibrentasvir vs sofosbuvir/velpatasvir across genotypes, and within subgroups defined by the presence or absence of cirrhosis and exposure to prior HCV treatments, results in small and non-significant differences in SVR12. There did not appear to be a trend favouring one treatment regimen over another.
- 6.16 The SVR12 rate for Arm E of MAGELLAN-1 was 91.5% [95% CI 79.6, 97.6], based on 44 patients with genotype 1 and three patients with genotype 4 HCV who had prior treatment with a direct acting antiviral regimen for HCV (including 34 patients who were NS5A experienced). The submission therefore claimed that glecaprevir/pibrentasvir is effective in this population. There is no evidence suggesting that PBS recommended regimen of sofosbuvir/velpatasvir is effective in this population.
- 6.17 [REDACTED] patients experienced virologic failure in the relevant arm (Arm E, 16 weeks duration of treatment) in MAGELLAN-1. All [REDACTED] patients were NS5A inhibitor experienced and three were experienced with both an NS5A inhibitor and an NS3/4A protease inhibitor. [REDACTED] patients were IL28B genotype CT or TT, and the [REDACTED] was not determined. All failed patients had baseline polymorphisms in NS5A. [REDACTED] patients had cirrhosis. Prior failure of treatment with an NS5A inhibitor may have selected patients with poor prognostic features (such as IL28B non-CC, cirrhosis and NS5A resistant polymorphisms).
- 6.18 In Arm E of MAGELLAN-1, 94% of patients had genotype 1. Therefore, for patients experienced on NS5A inhibitors, the clinical efficacy of glecaprevir/pibrentasvir in patients who have genotypes other than 1 is largely unknown.
- 6.19 The PSCR (p1-3) provided in vitro data for genotypes 2, 4, 5 and 6 suggesting that pibrentasvir retained activity against common NS5A substitutions that confer resistance. It also provided in vitro data that pibrentasvir retained activity against Y93H substitution, the more common substitution causing resistance to NS5A in genotype 3.

Comparative harms

6.20 The submission presented a summary of adverse event data as well as treatment emergent adverse events occurring in 10% or greater of patients in treatment arms for the included glecaprevir/pibrentasvir and sofosbuvir/velpatasvir study arms. An unadjusted comparison across studies for adverse events is presented in Table 6 below.

Table 6: Summary of adverse events reported in respective glecaprevir/pibrentasvir and sofosbuvir/velpatasvir studies

Outcome	GLE/PIB pooled N=1,308 n (%)	SOF/VEL pooled N=1,192 n (%)	GLE/PIB minus SOF/VEL % [95% CI] ^a
Any AE	871 (66.6)	939 (78.8)	-12.2 [-15.6, -8.7]
Any with reasonable possibility of being related to study drug	531 (40.6)	NR	-
Any SAE	59 (4.5)	28 (2.3)	2.2 [0.7, 3.6]
AE to leading to discontinuation of study treatment	5 (0.4)	2 (0.2)	p=0.311
Any fatal AE	2 (0.15)	NR	-
Deaths	4 (0.3)	3 (0.3)	p=0.798
Fatigue	196 (15.0)	250 (21.0)	-6.0 [-9.0, -3.0]
Headache	221 (16.9)	328 (27.5)	-10.6 [-13.9, -7.4]
Nausea	106 (8.1)	150 (12.6)	-4.5 [-6.9, -2.1]
Pruritus	61/663 (9.2)	16/491 (3.3)	5.9 [3.2, 8.6]
Diarrhoea	64/620 (10.3)	64/781 (8.2)	p=0.170
Nasopharyngitis	33/639 (5.2)	126/1,112 (11.3)	-6.2 [-8.7, -3.6]
Insomnia	31/677 (4.6)	86 (7.2)	-2.6 [-4.8, -0.5]
Asthenia	13/261 (5.0)	41/624 (6.6)	p=0.368

^aThe p-value is given for differences that are not statistically significant.

Differences calculated using the difference in proportions test (prtesti), Stata 14.1.

AE = adverse event; GLE/PIB = glecaprevir/pibrentasvir; SAE = serious adverse event; SOF/VEL = sofosbuvir/velpatasvir

Source: Table B-55, p171, Table B-56, p172, Table B-57, p173 and Table B-58, p174 of the submission.

6.21 There were, on average, fewer patients who experienced an adverse event in the glecaprevir/pibrentasvir study arms than in the sofosbuvir/velpatasvir studies; however more patients experienced a serious adverse event (SAE). The larger number of SAEs in the pooled glecaprevir/pibrentasvir results is partly driven by 25 patients who were reported to have had a SAE in EXPEDITION-4 (24% of all enrolled patients). EXPEDITION-4 was conducted in patients with kidney disease, with more than 80% requiring dialysis. The clinical study report states (p136) that none of the SAEs in this study were considered related to glecaprevir/pibrentasvir. Removing this study from the analysis resulted in a non-significant difference in the incidence of SAEs of 0.5% favouring sofosbuvir/velpatasvir. The safety of the drugs is likely to be similar.

Clinical claim

- 6.22 The submission claimed that glecaprevir/pibrentasvir is equivalent to sofosbuvir/velpatasvir in terms of efficacy and safety in subjects across all CHC genotypes. This claim is reasonable for the majority of patients.
- 6.23 For patients experienced with NS5A inhibitors:
- there is no clinical evidence for glecaprevir/pibrentasvir in genotypes other than 1; and
 - there is no evidence at all for the PBAC recommended sofosbuvir/velpatasvir regimens in any genotype.
- 6.24 The PSCR (p1) argued that the MAGELLAN-1 study included 3 genotype 4 patients with prior NS5A inhibitor experience treated with glecaprevir/pibrentasvir with all achieving SVR12.
- 6.25 The ESC noted most of the evidence of SVR12 in patients previously treated with an NS5A inhibitor was conducted in vitro. The ESC also noted it was unclear whether the first 40 patients in MAGELLAN-1 had genotypes that were resistant to an NS5A inhibitor, noting that failure is different from treatment resistance.
- 6.26 The PBAC considered that the claim of non-inferior comparative effectiveness across all CHC genotypes was reasonable for patients who are NS5A treatment naïve.
- 6.27 The PBAC considered that the claim of non-inferior comparative safety was reasonable.
- 6.28 As per the sponsor's request in its pre PBAC Response, the PBAC did not consider the efficacy and safety of glecaprevir/pibrentasvir in patients who are NS5A treatment experienced at this time.

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

Economic analysis

- 6.29 The submission presented a cost-minimisation analysis, and equi-effective doses are summarised in the table below.

Table 7: Equi-effective doses by genotype and/or prior treatment experiences

Patient population	Treatment duration	
	Glecaprevir 300 mg / pibrentasvir 120 mg	Sofosbuvir 400 mg / velpatasvir 100 mg
Treatment naïve		
Genotype 1-6, without cirrhosis	8 weeks	12 weeks
Genotype 1-6, with cirrhosis	12 weeks	12 weeks
Treatment experienced (NS5A inhibitor naïve)		
Genotype 1, 2, 4-6, without cirrhosis	8 weeks	12 weeks
Genotype 1, 2, 4-6 with cirrhosis	12 weeks	12 weeks
Genotype 3, with or without cirrhosis	16 weeks	12 weeks
Treatment experienced with NS5A inhibitor		
Genotype 1-6, with or without cirrhosis	16 weeks	12 weeks ^a

^aUnlikely to be used in this population. No current evidence for sofosbuvir/velpatasvir in patients who have failed NS5A inhibitors. Not supported by current guidelines^a.

Source: Table D-1, p184 of the submission.

- 6.30 The equi-effective doses are consistent with the results presented above. In patients who have failed a prior NS5A inhibitor, the comparison presented in the submission was 12 weeks of sofosbuvir/velpatasvir, although sofosbuvir/velpatasvir is not likely to be used in this setting.
- 6.31 For the purposes of the submission, the cost per patient for a 12 week course of sofosbuvir/velpatasvir was assumed to be \$ [REDACTED]. Should glecaprevir/pibrentasvir be listed on the PBS, it is anticipated that the effective price of glecaprevir/pibrentasvir will be equivalent to the price of sofosbuvir/velpatasvir.
- 6.32 The PSCR (p4) argued it can be assumed that the cost-effectiveness of glecaprevir/pibrentasvir in NS5A experienced patients would be similar to that already accepted by the PBAC for currently available DAA regimens.
- 6.33 The ESC noted that the final cost-minimisation calculations will need to be undertaken once the TGA recommended dosing regimens for each of the sub-populations above are known. The ESC also noted that a cost-minimisation approach against the currently listed DAA regimens would be appropriate given the PBAC's November 2016 recommendation for sofosbuvir/velpatasvir.
- 6.34 The ESC noted the cost-effectiveness of glecaprevir/pibrentasvir in NS5A treatment experienced patients has not been examined.

^a European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2016. Journal of hepatology 2017;66(1):153.

Drug cost/patient/course: \$ [REDACTED]

- 6.35 The submission assumed a “proxy” cost of \$ [REDACTED] for a 12 week course of sofosbuvir/velpatasvir and anticipates that the cost of glecaprevir/pibrentasvir will be equivalent to the cost of sofosbuvir/velpatasvir for a course of treatment.
- 6.36 In its consideration of sofosbuvir/velpatasvir the PBAC noted that “in the absence of demonstrated superior comparative effectiveness or comparative safety of sofosbuvir/velpatasvir FDC over alternative regimens, there is no basis for sofosbuvir/velpatasvir FDC to have a cost advantage over the relevant lowest priced regimen in the General Statement.” (Sofosbuvir/velpatasvir public summary document (PSD), November 2016).

Estimated PBS usage & financial implications

- 6.37 This submission was not considered by DUSC. The submission estimated the extent of use and financial implications of listing glecaprevir/pibrentasvir using a mixed epidemiological and market share approach.
- 6.38 The estimated extent of use and financial estimates are summarised below in Table 8.

Table 8: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number of patients treated	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Number of packs dispensed ^a	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated financial implications of glecaprevir/pibrentasvir					
Cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Copayments	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Cost to PBS/RPBS less copayments	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Estimated financial implications for substituted drugs					
Cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Copayments	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Cost to PBS/RPBS less copayments	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net financial implications					
Net cost to PBS/RPBS	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]

^a One pack supplies 4 weeks treatment, the submission assumed that [REDACTED]% of patients will be treated with 8 weeks regimen, [REDACTED]% will be treated with 12 weeks regimen and [REDACTED]% will be treated with 16 weeks regimen.
Source: Table E-8, Table E-9 and Table E-11 of the submission.

Financial Management – Risk Sharing Arrangements

- 6.46 The PBAC recommended that glecaprevir/pibrentasvir enter the Risk Sharing Arrangement (RSA) currently in place for other drugs used for the treatment of CHC, and be subject to the same subsidisation caps and rebate arrangements.

7 PBAC Outcome

- 7.1 The PBAC was of a mind to recommend the Authority Required General Schedule and Section 100 listing of glecaprevir with pibrentasvir for the treatment of chronic hepatitis C infection for patients with genotypes 1-6, with or without cirrhosis. However, the PBAC deferred making a final recommendation pending the provision of the relevant TGA delegate's overview.
- 7.2 The PBAC considered that the PBS restriction should be consistent with other DAA drugs listed in the General Statement for Drugs for the Treatment of Hepatitis C (*General Statement*), and considered that the maximum quantity should provide for one pack, and three repeats, allowing for up to 16 weeks treatment duration. The PBAC noted that the exact restriction would need to be aligned with the TGA registration of the drug.
- 7.3 The PBAC noted the sponsor's request for a streamlined authority listing; however, it did not agree that this was appropriate at this time. The PBAC preferred an authority required (telephone) listing on the basis of consistency with existing DAA PBS listings, which are currently all authority required (telephone). Further, the PBAC considered that a telephone authority would ensure GP prescribing consistency across the different treatment durations of glecaprevir/pibrentasvir (ranging from 8 weeks to 16 weeks for the specific patient groups).
- 7.4 The PBAC accepted sofosbuvir/velpatasvir as the appropriate comparator for patients with CHC genotypes 1-6, who are NS5A treatment naïve.
- 7.5 The PBAC considered that the claim of non-inferior comparative effectiveness across all CHC genotypes was reasonable for patients who are NS5A treatment naïve.
- 7.6 The PBAC considered that the claim of non-inferior comparative safety was reasonable.
- 7.7 As per the sponsor's request in its pre PBAC Response, the PBAC did not consider the efficacy and safety of glecaprevir/pibrentasvir in patients who are NS5A treatment experienced at this time.
- 7.8 The PBAC accepted that cost-minimisation against sofosbuvir/velpatasvir was

appropriate and noted that final cost-minimisation calculations would need to be undertaken once the TGA recommended dosing regimens for each of the sub-populations are known. The PBAC recalled that, in its consideration of sofosbuvir/velpatasvir, it had noted that “in the absence of demonstrated superior comparative effectiveness or comparative safety of sofosbuvir/velpatasvir FDC over alternative regimens, there is no basis for sofosbuvir/velpatasvir FDC to have a cost advantage over the relevant lowest priced regimen in the General Statement.” (Sofosbuvir/velpatasvir public summary document (PSD), November 2016)

- 7.9 The PBAC considered that the clinical evaluation presented by the submission – based on seven single-arm studies with glecaprevir/pibrentasvir and five studies with sofosbuvir/velpatasvir – supported the claim of non-inferior comparative efficacy and safety compared to sofosbuvir/velpatasvir. The PBAC noted that, on average, fewer patients on glecaprevir/pibrentasvir experienced adverse events compared with sofosbuvir/velpatasvir.
- 7.10 The PBAC considered that the availability of this regimen would likely have a considerable impact on prescribing choices for HCV treatment in Australia, as the committee anticipated that there would likely be a prescriber preference for another treatment regimen that can act against all genotypes.
- 7.11 The PBAC foreshadowed its intention to recommend that, under s101(3BA) of the *National Health Act 1953*, glecaprevir/pibrentasvir should be treated as interchangeable on an individual patient basis with sofosbuvir/velpatasvir and, by extension, the other medicines that PBAC considered interchangeable with sofosbuvir/velpatasvir at its November 2016 meeting.
- 7.12 The PBAC also foreshadowed its advice that glecaprevir/pibrentasvir should have the same nurse practitioner prescribing arrangements as other HCV treatments listed under the *General Statement*. Currently HCV treatments under the *General Statement* are listed for prescribing by authorised nurse practitioners under the General Schedule only. Medicines for the treatment of hepatitis C are not listed for prescribing by authorised nurse practitioners under the S100 Highly Specialised Drugs Program.
- 7.13 The PBAC foreshadowed its intention to recommend that the Early Supply Rule should apply.

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

Abbvie welcomes the PBAC recommendation for PBS listing of Maviret in NS5A naïve HCV patients