

An addendum to this minute has been included at the end of the document.

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

1 Purpose of Application

- 1.1 The minor submission requested an amendment to the General Statement for Drugs for the Treatment of Hepatitis C (the General Statement), to shorten the duration of treatment course of glecaprevir/pibrentasvir (GLE/PIB) from 12 weeks to 8 weeks for the treatment of patients with genotypes (GT) 1-6 chronic hepatitis C (CHC) who are treatment naïve (TN) with compensated cirrhosis (CC).

2 Background

Registration status

- 2.1 GLE/PIB was TGA registered on 2 January 2018 for the treatment of adult patients with CHC GT 1-6 infection with or without CC. This includes patients with GT1 infection who were previously treated either with a regimen of an NS5A inhibitor or with an NS3/4A protease inhibitor. On 18 December 2019, TGA registration was extended to include the adolescent population.
- 2.2 The TGA Delegate's Overview regarding the reduction of treatment duration was provided on 28 August 2020.

Previous PBAC consideration

- 2.3 GLE/PIB was recommended by the PBAC at its November 2017 meeting as a pan-genotypic treatment, on a cost minimisation basis with sofosbuvir/velpatasvir (SOF/VEL, Eplclusa[®]) and was listed on 1 August 2018.
- 2.4 GLE/PIB is currently listed on the PBS as Authority Required General Schedule and Section 100 listings for the treatment of GT1-6 CHC infection for TN and treatment experienced (TE) patients (including those with prior NS5A treatment) with or without CC. Current listings are outlined in the General Statement¹.

For more detail on PBAC's view, see section 6 PBAC outcome.

¹ <https://www.pbs.gov.au/info/healthpro/explanatory-notes/general-statement-hep-c>

3 Requested listing

- 3.1 The submission requested that the matrices of direct-acting antiviral (DAA) regimens within the General Statement be updated to change the duration of a course of GLE/PIB treatment GT1-6 CHC TN/CC patients from 12 weeks to 8 weeks. The requested change is shown in Table 1.

Table 1: Proposed revised treatment matrix

Hepatitis C – Cirrhotic patients ^a		
	Treatment naïve	Treatment experienced
All genotypes (Pan-genotypic regimens)	GLECAPREVIR + PIBRENTASVIR [12 weeks 8 weeks]	GLECAPREVIR + PIBRENTASVIR [12 or 16 weeks] ^b

^a GLE/PIB is not indicated for patients with decompensated cirrhosis.

^b Refer to 'General Statement for Drugs for the Treatment of Hepatitis C' for treatment-experienced patients' recommended GLE/PIB treatment durations, dependent on HCV genotype and specific prior failed treatment regimens. <https://www.pbs.gov.au/info/healthpro/explanatory-notes/general-statement-hep-c>

Source: Table 1 submission

- 3.2 The requested change would result in TN/CC patients utilising the 8-week PBS items for GLE/PIB (11332K, 11335P and 11353M) rather than the 12-week PBS items (11345D, 11346E and 11354N), however no change to individual PBS items would be required as the relevant requirements are outlined in the General Statement. The 12-week regimen will still be required for cirrhotic and non-cirrhotic patients with GT 1 who have failed an NS3/4A PI based regimen and for cirrhotic patients with GT 1, 2, 4, 5, 6 who have failed regimens containing peginterferon, ribavirin and/or sofosbuvir but no prior experience with an NS3/4A PI or NS5A inhibitor.

For more detail on PBAC's view, see section 6 PBAC outcome.

4 Comparator

- 4.1 The minor submission nominated the current twelve-week treatment regimen of GLE/PIB as the main comparator as this is the current PBS listed regimen.
- 4.2 The PBAC noted that any of the currently listed alternative pan-genotypic treatments were comparators for GLE/PIB, as well as noting that genotype specific treatments were secondary comparators – for individual patient subgroups within the broader population.

For more detail on PBAC's view, see section 6 PBAC outcome.

5 Consideration of the evidence

Sponsor hearing

- 5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

5.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

5.3 The minor submission was based on EXPEDITION-8: a single-arm, multicentre, phase 3b trial that included 343 GT1-6 TN CC CHC subjects with sustained virologic response at 12-weeks (SVR12) after the completion of the 8-week treatment course.

Table 2: Trials and associated reports presented in the re-submission

Trial ID	Protocol title/ Publication title	Publication citation
Non-randomised studies (single-arm Phase 3b study)		
EXPEDITON-8 NCT03089944 (clinicaltrials.gov identifier)	A Study of Glecaprevir (GLE)/Pibrentasvir (PIB) in Treatment-Naive Adults With Chronic Hepatitis C Virus (HCV) Genotype 1-6 Infection and Compensated Cirrhosis (EXPEDITION-8)	Brown et al. Glecaprevir/pibrentasvir for 8 weeks in treatment-naïve patients with chronic HCV genotypes 1-6 and compensated cirrhosis: The EXPEDITION-8 trial. J Hepatol. 2020 Mar;72(3):441-449. doi: 10.1016/j.jhep.2019.10.020. Epub 2019 Nov 2.

Comparative effectiveness

5.4 The outcomes of the EXPEDITION-8 trial showed high efficacy for per protocol (PP) analyses and the pooled genotype intention-to-treat (ITT), with 99.7% of the PP population (N=335) and 97.7% (N=343) of the ITT population achieving SVR12. The pooled genotype study results are presented in Table 3 below.

Table 3: EXPEDITION-8 SVR12 Efficacy endpoints – GT1-6

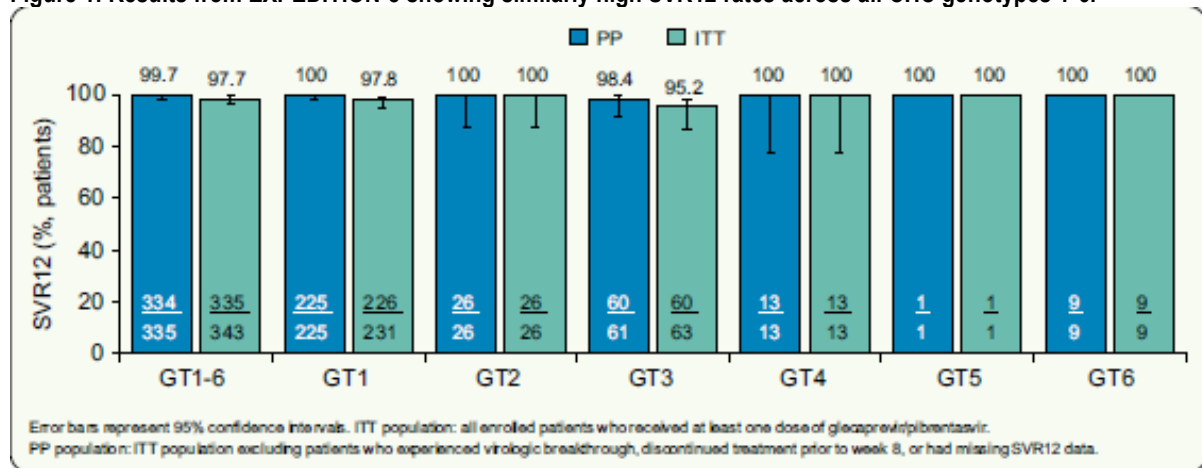
	GT1-6 PP Population	GT1-6 ITT Population
Patient population	N=335	N=343
SVR12	99.7%	97.7%
n/N	334/335	335/343
95% CI	98.3-99.9	96.1-99.3
Non-response*	1/335 (0.3%)	8/343 (2.3%)
Virologic failure	1/335 (0.3%)	1/343 (0.3%)
On-treatment virologic failure	0/335	0/343
Relapse	1/332 (0.3%)	1/336 (0.3%)
Non-virologic failure	0/335	7/343 (2%)
Premature discontinuation of study drug	0/335	1/343 (0.3%)
HCV re-infection	0/335	0/343
Missing SVR12	0/335	6/343 (1.7%)

* Non-responders; subjects not achieving SVR12 (includes both virologic failure and non-virologic failure)

Source: Table 4of submission

5.5 Genotype-specific results in TN/CC subgroups for GT 1-6 are shown in Figure 1.

Figure 1: Results from EXPEDITION-8 showing similarly high SVR12 rates across all CHC genotypes 1-6.



GT, genotype; HCV, hepatitis C virus; ITT, intention-to-treat; PP, per-protocol; SVR12, sustained virologic response at post-treatment week 12.

Source: Graphic 2 of the submission. Extracted from Brown et al 2020 (submission citation)

- 5.6 SVR12 rates of 100% were achieved for GT 1, 2, 4-6 in the PP population and 2 and 4-6 in the ITT population. Six patients in the ITT population were missing SVR12 data and were considered to have failed treatment. Five (1.8%) GT-1 patients were considered non-responders, none of which were virologic failures (Table 3). The lowest efficacy was found in the GT-3 population with 98.4% (60/61) and 95.2% (60/63) SVR12 in the PP and ITT populations, respectively. The TGA Delegate’s Overview expressed concerns regarding the adequacy of the data to support the use of the 8-week regimen in GT3 TN/CC patients and referred the matter to the ACM. Whilst the ACM supported registration of the 8-week treatment option for GT3 patients, the Committee also recommended that individualised decision-making should be left up to the prescriber for all 6 genotypes, by amending the treatment period to ‘8 or 12 weeks’ for GT1-6 TN/CC patients. The Pre-PBAC Response noted the TGA registration was not yet finalised and stated the details of the finalised registration would be provided as soon as it was made available.
- 5.7 The submission stated the SVR12 rates from EXPEDITION-8 are similar to those seen in the pooled GLE/PIB data previously presented to the PBAC, which found the proportion of subjects achieving SVR12 was 97.4% (n=1229/1262) in TN or TE subjects with GT1-6 with or without cirrhosis (para 6.12, glecaprevir/pibrentasvir Public Summary Document (PSD), July 2017 PBAC meeting).
- 5.8 The submission stated the SVR12 rates for the 8-week regimen in EXPEDITION-8 were also consistent with the 12-week regimen in the EXPEDITION-1 study. The SVR12 rate for the TN/CC subjects included in EXPEDITION-1 (N=110) was 100% (both ITT and PP populations; however EXPEDITION-1 did not include any GT3 patients). The submission argued it was reasonable to conclude that the SVR12 results of EXPEDITION-1 would be similar and consistent with the SVR12 rates in EXPEDITION-8 if GT-3 subjects were included in the EXPEDITION-1 study.

Comparative harms

5.9 EXPEDITION-8 found lower adverse rates for the 8-week GLE/PIB regimen compared to the 12-week course, potentially due to reduced overall treatment duration. The submission stated that the 8-week treatment course was well tolerated with no subjects discontinuing treatment due to adverse effects (AE), and no serious adverse effects (SAE) attributed to GLE/PIB. A comparison of safety outcomes for the 8-week and 12-week regimens is presented in Table 4.

Table 4: Treatment-emergent AEs in study EXPEDITION-8 vs. EXPEDITION-1

	EXPEDITION-8 8 weeks treatment duration		EXPEDITION-1* 12 weeks treatment duration	
	N=343	%	N=146	%
Subjects				
Any AE	158	46%	101	69%
Any AE grade ≥3	11	3%	NR	NR
Any serious AE (SAE)	6	2%	11	8%
Any drug-related SAE	0	0	0	0
Any drug-related AE grade ≥3	1	<1%	NR	NR
Any AE leading to discontinuation	0	0	0	0
Deaths (any cause)	0	0	1	1%
AEs occurring in ≥5% subjects:				
Fatigue	30	9%	28	19%
Pruritis	29	8%	14	10%
Headache	28	8%	20	14%
Nausea	19	6%	13	9%
Diarrhoea	-	-	12	8%
Urinary Tract Infection	-	-	9	6%

* EXPEDITION-1 was a single-arm open-label multicentre ph 3 trial of 12 weeks of GLE-PIB for adults with CC and CHC GT 1, 2,4,5,6

Abbreviations: NR = not reported

Source: Table 5 of submission

5.10 The submission argued no new safety signals were identified in EXPEDITION-8 and the safety profile was consistent with the established safety profile of GLE-PIB.

Clinical claim

5.11 The submission claimed non-inferior comparative effectiveness and safety of GLE/PIB for the 8-week treatment course compared to the 12-week course.

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

5.13 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

- 5.14 The minor submission requested the same cost for the 8-week course as the current cost of the 12-week course by application of the existing Special Pricing Arrangement (SPA), and no changes to the risk sharing arrangements.

Estimated PBS usage & financial implications

- 5.15 The minor submission estimated there to be no financial implications to the government in alignment with the PBAC's recommendation that the cost of a course of treatment should be set irrespective of treatment duration (para 7.15, Harvoni[®] PSD, March 2015 PBAC meeting). The submission further stated that this principle has been applied to DAA recommendations (para 7.2, Viekira Pak[®] PSD, July 2015 PBAC meeting; para 6.44, Zepatier[®] PSD, July 2016 PBAC meeting).
- 5.16 The submission estimated an increased market share for GLE/PIB as the submission assumed patients would prefer an 8-week treatment course and the equivalent treatment course for the alternative pan-genotypic treatment (SOF/VEL) is 12 weeks. The submission noted GLE/PIB was listed on a cost minimisation basis with SOF/VEL.
- 5.17 The minor submission estimated a net save to the PBS budget (at published price) of \$10 million to < \$20 million in Year 1 decreasing to a saving of \$0 to < \$10 million in Year 6 as the prevalent population with CHC reduces. This is summarised in the Table 5 as well as the expected prescription numbers.

Table 5: Estimated use and financial implications (published price)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Estimated financial implications of Maviret						
to PBS	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ³	\$█ ³
to RPBS	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴
to PBS/RPBS	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ³	\$█ ³
Estimate financial implications of other impacted medicines						
to PBS	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵
to RPBS	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵
to PBS/RPBS	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵
Net financial implications						
to PBS	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵
to RPBS	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵
to PBS/RPBS	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵

Source: Maviret utilisation and cost model workbook attachment.

The redacted values correspond to the following ranges

¹ 500 to < 5,000

² \$20 million to < \$30 million

³ \$10 million to < \$20 million

⁴ \$0 to < \$10 million

⁵ net cost saving

5.18 The submission claimed that there would be no change in the net financial impact to government, noting that a set cost per treatment course (irrespective of duration) is administered through the current Deed of Agreement.

5.19 As a minor submission, the financial estimates have not been independently evaluated.

Quality Use of Medicines

5.20 The sponsor stated that a reduction in the duration of therapy while maintaining efficacy at reduced patient cost is consistent with Quality Use of Medicines principles.

5.21 The sponsor reiterated that an 8-week treatment duration has non-inferior comparative effectiveness to the 12-week treatment, as well as reducing patient visits to the pharmacy and cost to the patient. The sponsor also claimed reduced treatment duration regimens would improve adherence.

For more detail on PBAC's view, see section 6 PBAC outcome.

6 PBAC Outcome

6.1 The PBAC was of a mind to recommend the listing of an 8-week treatment option of glecaprevir with pibrentasvir (GLE/PIB) for the treatment of chronic hepatitis C (CHC) infection in patients who are treatment-naïve with compensated cirrhosis (TN/CC), however deferred making a recommendation to amend the General Statement for Drugs for the Treatment of Hepatitis C (the General Statement) pending finalisation of

the TGA registration. The PBAC noted the Advisory Committee for Medicines (ACM) supported registration of the 8-week regimen for patients with genotype 3 infection, however also recommended retaining the 12-week regimen as an option for the TN/CC population to allow for individual clinical decision-making. As there was residual uncertainty as to whether the 12-week regimen would remain as part of the TGA registration, the PBAC decided to defer making a recommendation until the final TGA outcome was known.

- 6.2 The PBAC was of a mind to retain the 12-week regimen option if it remains part of the TGA registration. The Committee advised that this regimen should be included as a footnote to the General Statement for simplicity and reaffirmed that any change to treatment options within the General Statement that achieve the same health outcomes must be at no increase in the average cost to the Government. The PBAC considered that there may be a small number of patients utilising the 12-week treatment regimen as physician and patient preference would most likely be for the 8-week treatment regimen.
- 6.3 The PBAC noted the EXPEDITION-8 trial presented in the submission demonstrated the 8-week regimen of GLE/PIB achieves similar efficacy outcomes to the 12-week regimen, in terms of sustained virological response rates at week 12 (SVR12). The PBAC noted there was one case of virological failure in GT3 and some patients were lost to final follow-up, however noted GT3 is known to be more difficult to treat and considered the missing data would likely not alter its overall conclusions with regards to efficacy outcomes.
- 6.4 The PBAC considered that the comparative harms of the 8-week treatment regimen were consistent with the known safety profile of GLE/PIB and appeared no worse than the 12-week treatment regimen.
- 6.5 The PBAC noted that the sponsor estimated a net save in published PBS expenditure, however no net financial impact at the effective price level. The Committee noted reduced treatment durations would result in a reduced number of co-payments for patients. The Committee also considered that since the cost per course of treatment would remain the same (as administered through the current Deed of Agreement), the introduction of an 8-week regimen should not increase the effective net cost to government.

Outcome:
Deferred

7 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the

listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

8 Sponsor's Comment

AbbVie thanks the PBAC for its consideration of this item to reduce the duration of a treatment course for this sub-group of chronic hepatitis C patients.

Addendum to the November 2020 PBAC Minutes:

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

9 Background and current situation

- 9.1 At its November 2020 meeting, the PBAC deferred making a recommendation on the request to amend the listing of glecaprevir with pibrentasvir (GLE/PIB) to shorten the duration of treatment course from 12 weeks to 8 weeks for patients with genotypes (GT) 1-6 chronic hepatitis C (CHC) who are treatment naïve (TN) with compensated cirrhosis (CC). The deferral was due to uncertainty as to whether the 12-week regimen would be retained in the TGA registration for this population.
- 9.2 At time of consideration, the PBAC noted the Advisory Committee for Medicines (ACM) supported registration of the 8-week regimen, however also recommended retaining the 12-week regimen as an option for the TN/CC population to allow for individual clinical decision-making. As there was residual uncertainty as to whether the 12-week regimen would remain as part of the TGA registration, the PBAC decided to defer making a recommendation until the final TGA outcome was known.
- 9.3 Following the November 2020 meeting, the sponsor of GLE/PIB, AbbVie Pty Ltd, advised the TGA had finalised the registration and Product Information, which included retention of the 12-week treatment regimen for TN/CC patients as an option, 'at the discretion of the prescriber'.

10 PBAC Outcome

- 10.1 The PBAC recommended amending the listing of glecaprevir with pibrentasvir (GLE/PIB) to include an 8-week treatment option for the treatment of chronic hepatitis C (CHC) infection in patients who are treatment-naïve with compensated cirrhosis (TN/CC). The PBAC's recommendation was based on, among other matters, its assessment that an 8-week regimen of GLE/PIB in TN/CC patients achieves similar therapeutic outcomes to the currently PBS-listed 12-week regimen.
- 10.2 In making this recommendation, the PBAC noted the TGA registration had now been finalised, which included retention of the 12-week regimen for the TN/CC population as an option for use at the discretion of the treating clinician. Consistent with its view expressed at its November 2020 meeting, the PBAC agreed that this regimen should be retained as an option and included as a footnote to the General Statement for

simplicity. The PBAC reaffirmed its view that there may be a small number of patients utilising the 12-week treatment regimen as physician and patient preference would most likely be for the 8-week treatment regimen.

- 10.3 The PBAC noted the change to listing could be achieved through an amendment to the General Statement and that changes to individual PBS item codes were not required.
- 10.4 The PBAC reaffirmed its view that based on the evidence presented, an 8-week regimen of GLE/PIB achieves similar efficacy and safety outcomes to a 12-week regimen in TN/CC patients.
- 10.5 The PBAC reaffirmed its view that any change to treatment options within the General Statement that achieve the same health outcomes must be at no increase in the average cost to the Government. Further, the PBAC also reaffirmed its advice that the introduction of an 8-week regimen should not increase the effective net cost to government and noted reduced treatment durations would result in a reduced number of co-payments for patients who receive an 8-week course.

Outcome:

Recommended

11 Recommended listing

- 11.1 Amend the General Statement for Drugs for the Treatment of Hepatitis C as follows (wording mirrors approved Product Information):

Hepatitis C – Cirrhotic patients ^a		
	Treatment naïve	Treatment experienced
All genotypes (Pan-genotypic regimens)	GLECAPREVIR + PIBRENTASVIR [12 weeks 8 weeks] ⁸	GLECAPREVIR + PIBRENTASVIR [12 or 16 weeks]

⁸ GLECAPREVIR + PIBRENTASVIR – A treatment duration of 12 weeks may be considered for patients with compensated cirrhosis, at the discretion of the prescriber.

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

12 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

13 Sponsor's Comment

AbbVie welcomes the decision of the PBAC and is working with the Department of Health on the earliest possible listing.