

5.08 TENOFOVIR ALAFENAMIDE, Tablet 25 mg, Vemlidy[®], Gilead Sciences

1 Purpose of Application

- 1.1 Section 100 (Highly Specialised Drug) Community Access Authority Required listing for tenofovir alafenamide (TAF) for treatment of chronic hepatitis B infections.

2 Requested listing

- 2.1 The requested restrictions were identical to the current PBS listing for tenofovir disoproxil fumarate (TDF) and similar to entecavir in chronic hepatitis B (CHB). The differences between the current restrictions for TDF and entecavir are that the TDF restriction has additional clinical criteria which states that patients must be nucleoside naïve, TDF must be the sole PBS-subsidised therapy for CHB, and a note that states patients may receive the treatment in combination with lamivudine but not with other PBS-subsidised antihepadnaviral therapy. Despite the additional criteria, the intent of the TDF and entecavir restrictions are the same and would likely cover the same patient populations. TDF and TAF are both prodrugs of tenofovir, but have different pharmacokinetic profiles.
- 2.2 In summary, listing was requested for TAF in adult patients with treatment-naïve and treatment-experienced CHB infections, with or without cirrhosis (presented over four separate restrictions. The requested restrictions, although narrower, were generally in line with the proposed TGA indication of TAF and concurred with the populations of the main trials supporting the submission (Study 108 and 110).
- 2.3 The basis for requesting listing of TAF was a cost minimisation analysis versus TDF.

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

3 Background

- 3.1 **TGA status at time of PBAC consideration:** the submission was submitted under the TGA/PBAC Parallel Process. TAF was registered on the ARTG on 22 February 2017 for the treatment of chronic hepatitis B in adults.
- 3.2 TAF had not been considered previously by the PBAC for chronic hepatitis B infections. However, TAF, as part of fixed dose combinations with other antivirals (TAF 25 mg + emtricitabine 200 mg and TAF 10 mg + emtricitabine 200 mg + elvitegravir 150 mg + cobicistat 150 mg) are currently PBS listed for the management of HIV infections. In that consideration, the PBAC accepted that TAF should be considered a different drug to TDF for the purposes of Section 85(2) of the Act. (p3, 4.07 tenofovir alafenamide + emtricitabine + rilpivirine PBAC PSD, November 2016)

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

4 Clinical place for the proposed therapy

- 4.1 Hepatitis B is a blood-borne virus. It is transmitted via contact with infectious blood, semen and body fluids. Whilst a vaccine exists for hepatitis B, chronic hepatitis B virus (CHB) infections remains a significant burden as it is currently incurable and is a main cause of liver inflammation, cirrhosis and cancer. Treatments for CHB are usually lifelong, the goal of viral suppression therapy is to delay onset of liver inflammation, cirrhosis and cancer and as a result bring about improvements in patient survival and quality of life.
- 4.2 TAF presents another treatment option alongside TDF and entecavir in first line therapy of chronic hepatitis B infections, as well as an alternative in cases where the patient has developed resistance to lamivudine.

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

5 Comparator

- 5.1 TDF was nominated as the appropriate comparator. However, the evaluation noted that other nucleotide/nucleoside analogues, such as entecavir and adefovir, could also be appropriate comparators. The Pre-Sub-Committee Response (PSCR) argued that the decision to use entecavir or adefovir would precede the choice between TDF and TAF. The PBAC considered that although there would be a proportion of TAF substituting for TDF, it was also likely that TAF would substitute for entecavir in clinical practice. The PBAC therefore considered that entecavir was also an appropriate comparator.
- 5.2 Adefovir was not considered a comparator by the PBAC as it is no longer recommended as a first line therapy in clinical guidelines. Lamivudine was also not considered to be a comparator to TAF as it is more likely that prescribers will add TAF to lamivudine (in those with declining response) rather than replacing lamivudine with TAF (or TDF as it currently stands). Despite being available on the PBS as a sole treatment for CHB, lamivudine is not recommended as first line therapy in clinical guidelines.

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 health care professionals (1) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with TAF including a perceived better safety profile of TAF compared to TDF. The organisations, Hepatitis NSW and the Korean Hepatitis B Education Project, indicated their view that there were fewer side effects in terms of both bone mineral density and kidney function in TAF compared to TDF, and that access to TAF may help to increase HBV treatment rates.

Clinical trials

- 6.3 The submission was based on two head-to-head trials that compared TAF to TDF in patients with CHB infections (Study 108 and Study 110, n=1301). The trials were identical in their eligibility criteria except that Study 108 had recruited patients who were HBeAg negative whereas Study 110 recruited patients who were HBeAg positive at screening. Adult patients with either treatment-naïve or treatment-experienced CHB infections, with or without cirrhosis were eligible for enrolment into the trials; this concurred with the requested restrictions. In addition, one single arm study (Study 1249, n=79) in patients with HIV and CHB coinfection was also included as supplementary evidence, mainly to illustrate safety of switching patients from TDF to TAF.
- 6.4 Details of the trials presented in the submission are provided in the table below.

Table 1: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
Study 108	A Phase 3, Randomised, Double-Blind Study to Evaluate the Safety and Efficacy of Tenofovir Alafenamide (TAF) 25mg QD versus Tenofovir Disoproxil Fumarate (TDF) 300 mg QD for the Treatment of HBeAg-Negative, Chronic Hepatitis B. Interim Week 48 Clinical Study Report Buti et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial	30 November 2015 The Lancet Gastroenterology & Hepatology 2016; Vol 1(3):p196-206
Study 110	Description: A Phase 3, randomised, Double-Blind Study to Evaluate the Safety and efficacy of Tenofovir Alafenamide (TAF) 25 mg QD versus Tenofovir Disoproxil Fumarate (TDF) 300 mg QD for the Treatment of HBeAg Positive Chronic Hepatitis B. Interim Week 48 Clinical Study Report Chan et al. •Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial	21 December 2015 The Lancet Gastroenterology & Hepatology 2016; Vol 1(3):p185-195
Supplementary study		
Study 1249	A Phase 3b Open-label Study of the Efficacy and Safety of Elvitegravir /Cobicistat /Emtricitabine /Tenofovir Alafenamide Single-Tablet Regimen in HIV-1/Hepatitis B Co-infected Adults. Interim Week 48 Clinical Study Report Gallant et al. Efficacy and Safety of Switching to a Single-Tablet Regimen of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (Genvoya) in HIV-1/Hepatitis B Co-infected Adults.	29 August 2015 Journal of Acquired Immune Deficiency Syndrome 2016, Vol 73 (3): 294-298

Source: Table B-3, p53 of the submission.

The key features of the direct randomised trials are summarised in Table 2.

Table 2: Key features of the included evidence

Trial	N	Treatment arms	Design/ duration	Risk of bias	Patient population	Outcome
Study 108	426	TAF25 mg od, n=285 TDF300mg od, n=141	MC, R, DB, 144 weeks (primary outcome at 48 weeks)	Low	HBeAgg negative	Primary outcome: Proportion of patients with plasma HBV DNA < 29 IU/mL
Study 110	875	TAF25 mg od, n=582 TDF300mg od, n=293	MC, R, DB, 144 weeks (primary outcome at 48 weeks)	Low	HBeAg positive	
Study 1249	79	elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg daily	OL single arm, 48 weeks	High	HIV/HBV coinfection	

DB=double blind; OL=open label; OS=overall survival; MC= multicentre; R=randomised; HBeAg = hepatitis B envelope antigen, HIV = human immunodeficiency virus, HBV = hepatitis B virus; od=oral daily.

Source: compiled during the evaluation

- 6.5 Study 108 was a double blind randomised trial of 426 adult patients who had HBeAg negative chronic hepatitis B, randomised in a 2:1 ratio to receive either treatment with TAF 25 mg once daily (n=285) or TDF 300 mg once daily (n=141) for 96 weeks, followed by 48 weeks of open label treatment for a total of 144 weeks. Similarly, Study 110 was a double blind randomised study which enrolled 875 adult patients who had HBeAg positive chronic hepatitis B, randomised in a 2:1 ratio to receive either treatment with TAF 25 mg once daily (n=582) or TDF 300 mg once daily (n=293) for 96 weeks, followed by 48 weeks of open label treatment for a total of 144 weeks. The primary outcome of the trials of proportion of patients with plasma HBV DNA < 29 IU/mL were measured after 48 weeks of treatment.
- 6.6 Study 1249 was an open label, single arm study that recruited 79 patients, of which four were HIV/HBV coinfecting adults who were HIV and HBV treatment naïve and 75 were HIV/HBV coinfecting adults who were HIV suppressed (with or without HBV DNA suppression). All patients were treated with a single tablet fixed dose combination of elvitegravir 150 mg/cobicistat 150 mg/ emtricitabine 200 mg/tenofovir alafenamide 10 mg once daily for 48 weeks.
- 6.7 The trials were balanced with respect to patient demographics except that in Studies 108 and 110, more patients randomised to TAF treatment were younger than 50 years at baseline compared to patients randomised to receive TDF, with a difference of 13% (p=0.015) and 5% (p=0.078), respectively. This imbalance may have biased the results of trials in favour of TAF particularly for outcomes that are age related, such as renal function decline or bone mineral density degradation, which were relied on by the submission for its safety claim.

Comparative effectiveness

- 6.8 The main outcome for Study 108 and 110 was viral response defined as a proportion of patients who had plasma HBV DNA less than 29 IU/mL at Week 48 of treatment. This was also the main outcome relied on for the clinical claim. The results from the trials are summarised in Table 3.

Table 3: Proportion of patients with plasma HBV DNA <29IU/mL in Study 108 and Study 110 at Week 48

Trial ID	TAF 25 mg n/N (%) [95% CI]	TDF 300 mg n/N(%) [95% CI]	Difference in proportion ¹ (95% CI)
Patients with chronic HBV infection, HBeAg negative (Study 108)			
Week 48	268/285 (94.0) [90.6, 96.5]	130/140 (92.9) [87.3, 96.5]	1.8 (-3.6%, 7.2%)
Week 72	40/42 (95.2) [83.8, 99.4]	22/23 (95.7) [78.1, 99.9]	NR
Patients with chronic HBV infection, HBeAg positive (Study 110)			
Week 48	371/581 (63.9) [59.8, 67.8]	195/292 (66.8) [61.1, 72.2]	-3.6 (-9.8%, 2.6%)
Week 72	121/155 (78.1) [70.7, 84.3]	53/73 (72.6) [60.9, 82.4]	NR

Abbreviation: TAF = tenofovir alafenamide, TDF = tenofovir disoproxil fumarate, HBV = hepatitis B virus, HBeAg = hepatitis B envelope antigen, NR = Not reported

Analysed in ITT population with missing = failure algorithm.

¹Difference in the proportion between treatment groups and its 95% CI were calculated based on the Mantel-Haenszel proportions adjusted by baseline HBV DNA categories and OAV treatment status strata.

Source: Table B-13, p81 of the submission, Table B-14, p83 of the submission, Table 14.2, p227 study 108 CSR and Table 14.2, p257 study 110 CSR

- 6.9 There were no statistically significant differences between TAF and TDF in the proportions of patients who attained HBV DNA<29IU/mL in Study 108 or 110 at Week 48. For this outcome, the submission had nominated a non-inferiority margin of

10%. As the lower 95% CIs did not exceed -10%, the submission claimed the results supported that TAF is non-inferior to TDF. The PBAC previously accepted a 10-15% non-inferiority margin for a similar, but not identical, outcome of the proportion of patients with HBV DNA <300 copies/mL in CHB infections (TDF Public Summary Document (PSD), July 2009). In that consideration, the PBAC accepted the claim that TDF 300 mg was no worse than entecavir 0.5 mg for treatment naïve patients and no worse than adefovir 10 mg for treatment experienced patients (TDF PSD, July 2009, p7). The ESC considered the nominated non-inferiority margins to be appropriate and that on the basis of the trial evidence presented, TAF appeared to be non-inferior to TDF. The PBAC agreed with the ESC that the nominated non-inferiority margin was appropriate, and noted that although the confidence interval for HBeAg positive patients was very close to the 10% limit, the data supported the claim that TAF was non-inferior to TDF.

- 6.10 There was no evidence of virological resistance to either TDF or TAF from the trials, however the trials were limited to a maximum of 144 weeks of follow up whereas the treatments are intended to be lifelong.

Comparative harms

- 6.11 The overall rate of adverse events was similar in both TAF and TDF treatment arms of Study 108 and 110. One death was reported in each trial but neither was considered to be treatment emergent.
- 6.12 The submission presented detailed comparisons of bone and renal safety outcomes from Study 108 and Study 110. The results of percentage change from baseline to Week 48 in Hip and Spine BMD are summarised in Table 4.

Table 4: Percentage change from baseline in Hip and Spine BMD at Week 48

Measure, Mean(SD)	Study 108			Study 110		
	TAF 25 mg	TDF 300 mg	Difference ¹ (95% CI)	TAF 25 mg	TDF 300 mg	Difference ¹ (95% CI)
Hip BMD						
Baseline	0.953 (0.16), n=283	0.938 (0.14), n=140	0.015 (-0.016, 0.046)	0.957 (0.14), n=568	0.960 (0.14), n=286	-0.002 (-0.023, 0.018)
% change Week 48 ²	-0.288% (2.14), n=270	-2.156% (2.17), n=133	1.868% (1.420, 2.317)	-0.100% (2.29), n=537	-1.715% (2.57), n=271	1.615% (1.265, 1.964)
Spine BMD						
Baseline	1.050 (0.19), n=284	1.033 (0.18), n=140	0.017 (-0.021, 0.055)	1.059 (0.16), n=572	1.061 (0.16), n=286	-0.002 (-0.025, 0.022)
% change Week 48 ²	-0.876 (2.86), n=271	-2.514% (3.36), n=133	1.638% (1.007, 2.268)	-0.417% (2.93), n=543	-2.294% (3.13), n=274	1.877% (1.440, 2.313)
FRAX analysis						
10 year hip fracture risk	0.79% (1.04)	0.84% (1.06)	NR	0.72% (1.68)	0.67% (0.91)	NR
10 year major osteoporotic fracture risk	3.72% (2.53)	3.83% (2.65)	NR	3.13% (2.66)	3.25% (2.25)	NR

Abbreviation: TAF = tenofovir alafenamide, TDF = tenofovir disoproxil fumarate, BMD = bone mineral density, NR = not reported

¹ Difference of Least-squared mean

² % change = change from baseline at a post baseline/baseline × 100%

Text in bold indicates statistically significant values

Source: Table B-25, p103-104 and Table B-26, p104-105, p115 of the submission

- 6.13 The measured decline in BMD from baseline to Week 48 was less for patients treated with TAF than those treated with TDF in the trials. The PBAC noted that although the differences between treatments were statistically significant, their magnitudes were small (<2% difference between the treatment arms) and believed it was unlikely that this would have any clinical benefit. The difference in BMD also did not translate into any differences in fracture events during the trials (8 total events between all patients, with 6 events associated with known trauma). The estimated 10 year fracture probability (based on FRAX analysis) for both TDF and TAF were also low and did not significantly differ between TAF and TDF, which indicated TAF treatment is unlikely to deliver any clinically meaningful bone safety benefits over TDF. Patients in the TDF arm of the trials were also significantly older (i.e. greater proportion over 50 years), given BMD decay generally increases with age, this also favoured TAF. The PBAC agreed with the ESC that the difference in BMD between patients treated with TAF and TDF was minimal, and that this did not result in a significant difference in fracture risk.
- 6.14 Table 5 summarises changes in serum creatinine and estimated glomerular filtration rate at Week 48 and 72 in Study 108 and 110.

Table 5: Measures of renal function in Study 108 and Study 110 (combined)

Renal function measurements	Week 48			Week 72		
	TAF (N=828)	TDF (N=418)	Mean difference ¹	TAF (N=818)	TDF (N=399)	Mean difference ¹
Change from baseline in serum creatinine (mg/dL), mean(SD)	0.010 (0.1140)	0.024 (0.0974)	0.014, P=0.012²	0.009 (0.0933)	0.016 (0.0911)	0.007, P=0.11 ²
Change from baseline in eGRFCG (mL/Min), median (Q1,Q3)	-1.2 (-8.4, 7.3)	-5.1 (-12.0, 3.0)	3.9 p <0.001³	-0.6 (-9.0,7.8)	-4.2 (-12.0,3.6)	3.6 p<0.001³

Abbreviation: TAF = tenofovir alafenamide, TDF = tenofovir disoproxil fumarate, eGRFCV = estimated glomerular filtration rate according to Cockcroft-Gault formula

¹Mean difference calculated during evaluation as simple arithmetic difference in the point estimate of TAF minus point estimate of TDF.

²P values from ANCOVA model including treatment as fixed effect and baseline serum creatinine as covariate

³P values from 2-sided Wilcoxon rank sum test to compare the two treatment groups

Text in bold indicate statistical significantly differences

Source: Table B-33, p118 of the submission

- 6.15 The PBAC noted that patients treated with TDF experienced slightly greater decrease in serum creatinine (SeCr) from baseline to Week 48 compared to patients treated with TAF. This difference was statistically significant for both mean and median differences at Week 48, but was not statistically significant at Week 72 for mean differences. This anomaly was not explained by the submission; however continued renal function declines would normally have been expected if there is a true difference between TAF and TDF in renal toxicity. Similarly, the PBAC also noted that although there was a statistically significant mean difference in eGRFCG levels between TAF and TDF, the mean difference did not appear to increase over time.
- 6.16 No other relevant safety issues were identified by the submission from any regulatory publications or other clinical studies of TAF. Post-marketing safety data was not presented by submission because at the time of making the submission, TAF as a single agent was unregistered in Australia and internationally.
- 6.17 Although statically significant, the magnitude of difference between TAF and TDF in the safety outcomes relating to BMD, fracture risk, and SeCR, was small and unlikely to translate to any clinically meaningful differences. The PSCR and pre-PBAC response argued that given the submission does not request a price premium for TAF over TDF on the basis of a comparative safety benefit, the magnitude of the accepted safety benefit is of diminished importance in PBAC’s decision-making but that the reduced impact of TAF on biomarkers of long-term renal and bone toxicities is relevant in the context of long-term safety for a chronic therapy.
- 6.18 There was a statistically significant difference (p=0.017) in hepatocellular carcinoma (HCC) events in patients treated with TAF (1 total event) and patients treated with TDF (5 total events). However, given the small number of events, the short duration of follow up, as well as the significant differences in age between patients treated with TDF and TAF, the ESC considered that it was unreasonable to draw conclusions from these trials on the relative effect of TAF and TDF treatments on the incidence of HCC but that this may warrant further investigation. Table 6 summarises the subject characteristics in Study 108 and Study 110. All subjects were Asian, treatment-naive and had a FibroTest® score at baseline consistent with severe fibrosis or cirrhosis

(range: 0.59 to 0.91). The pre-PBAC response agreed with the ESC and stated that serious adverse events will continue to be reported as a matter of course.

Table 6: Summary of Subjects with HCC across the Phase 3 Safety Population in Study 108 and Study 110

Study	Study Drug	Age (years)	Sex	HBV GT	AFP (IU/mL)	Cirrhosis History	FBT at BL	Onset (Day)
108	TAF	52	M	C	5.6	UNK	0.59	253
108	TDF	46	M	B	24.6	Yes	0.64	460
108	TDF	52	F	D	5.3	No	0.69	105
108	TDF	51	M	C	14.7	Yes	0.91	378
110	TDF	52	M	C	25	Yes	0.77	174
110	TDF	59	M	C	19.4	Yes	0.66	180

Source: Regulatory dossier, Module 2.7.4: p62, Table 24.

Abbreviations: AFP = alfa-fetoprotein; BL = baseline; F = female; FBT = FibroTest; GT = genotype; ID = identification; M = male; UNK = unknown

Benefits/harms

- 6.19 There are no expected clinically meaningful differences between TAF and TDF in efficacy and safety when used in the management of CHB infections.

Clinical claim

- 6.20 The submission described TAF as non-inferior in terms of comparative effectiveness and superior in terms of comparative safety over TDF. The ESC considered that the claim was reasonable with respect to efficacy but the claim of superior safety of TAF over TDF was based on surrogate measures (BMD and renal function), and the results were not consistent at all measured time points. The clinical relevance of the small but statistically significant differences in these surrogate outcomes was not established by the submission.
- 6.21 Given the data presented, the ESC considered that treatment with TAF is likely to be at least non-inferior in terms of safety compared to treatment with TDF.
- 6.22 The PBAC considered that the claim of non-inferior comparative effectiveness over TDF was reasonable, but that the claim of superior safety compared to TDF was not adequately supported by the data. The PBAC agreed with the ESC that TAF was at least non-inferior to TDF in terms of comparative safety.
- 6.23 The PBAC recalled it had previously recommended tenofovir disoproxil fumarate 300 mg for listing for use in CHB on a cost minimisation basis with adefovir 10 mg (nucleos(t)ide experienced) and entecavir 500 mcg (nucleos(t)ide naïve) (TDF PSD, July 2009). Similarly, entecavir 1 mg had been cost minimised to adefovir 10 mg in nucleoside experienced patients (entecavir PSD, July 2006). Therefore, the PBAC considered that TAF could also be considered to be non-inferior in terms of comparative effectiveness and safety to entecavir.

Economic analysis

- 6.24 The submission presented a cost minimisation analysis between TAF and TDF.
- 6.25 The PBAC noted it could only recommend listing TAF at a higher price than an alternative therapy or therapies if it is satisfied that it provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies. The alternative therapies in this case include entecavir. As noted above, the PBAC considered that TAF could be considered to be non-inferior in terms of comparative effectiveness and safety to entecavir.
- 6.26 The PBAC considered the equi-effective doses for the purposes of the cost-minimisation to be 0.5 mg entecavir to 25 mg TAF for nucleos(t)ide naïve patients and 1 mg entecavir to 25 mg TAF for nucleos(t)ide experienced CHB patients. The PBAC recommended a weighted price approach based on the current proportion of PBS utilisation for entecavir 0.5 mg and 1 mg, to account for the different equi-effective doses for the treatment of CHB in nucleoside analogue naïve patients (0.5 mg entecavir) and patients who have failed previous antihepadnaviral therapy (1 mg entecavir).

Table 7: Price calculations for maximum dispensed quantity of TAF 25 mg

Item	TAF 25 mg	TDF 300 mg	Entecavir 0.5 mg	Entecavir 1 mg	Adefovir 10 mg
Setting	HSD (Community Access)				
PBS code	-	10310P	10279B	10353X	10290N
AEMP (30 tablets)	\$458.95	\$458.95	\$306.68	\$498.70	\$525.00
Wholesaler mark-up	-	-	-	-	-
Price to pharmacist (30 tablets)	\$458.95	\$458.95	\$306.68	\$498.70	\$525.00
Pharmacist mark-up	\$36.72 (4%)	\$36.72 (4%)	\$24.53 (4%)	\$40.00	\$40.00
Dispensing fee	\$7.02	\$7.02	\$7.02	\$7.02	\$7.02
DPMQ (60 tablets)	\$961.64	\$961.64	\$644.92	\$1044.42	\$1097.02

Abbreviation: TAF = tenofovir alafenamide, TDF = tenofovir disoproxil fumarate, AEMP = approved ex-manufacturer price, DPMQ = Dispensed Price for Maximum Quantity
 Values for entecavir and adefovir were added during evaluation
 Source: Table D-1, p137 of the submission, PBS online schedule

Drug cost/patient/year:

- 6.27 \$5,769.84 assuming 6 scripts of 60 TAF 25 mg tablets (at a dose of 1 tablet a day). This is the same as the current drug cost/patient/year for TDF 300 mg at a dose of 1 tablet a day.
- 6.28 The PBAC noted that the cost per year of TAF will need to be recalculated on the basis of the cost-minimisation recommendation with entecavir.

Estimated PBS usage & financial implications

6.29 This submission was not considered by DUSC. The submission used a market share approach for the financial estimates, assuming substitution from TDF to TAF.

Table 8: Estimated extent of use and financial impact of TAF and sensitivity analyses

	2017	2018	2019	2020	2021
Financial estimates					
Forecasted TDF scripts (2 packs) for HBV					
Uptake/substitution rate of TAF	%	%	%	%	%
Estimated TAF scripts (2 packs)					
Total cost of TAF in submission ¹	\$	\$	\$	\$	\$
Total copayment ²	\$	\$	\$	\$	\$
Net cost of TAF scripts	\$	\$	\$	\$	\$
Cost offset from switching from TDF ¹	\$	\$	\$	\$	\$
MBS offset for TDF ³	\$	\$	\$	\$	\$
Total cost from switching in submission⁴	-\$	-\$	-\$	-\$	-\$
Sensitivity analyses					
20% Increase uptake of TAF (48% year 1 to 96% year 5)	-\$	-\$	-\$	-\$	-\$
20% Decrease uptake of TAF (32% year 1 to 64% year 5)	-\$	-\$	-\$	-\$	-\$
Increase MBS cost offset by 20%	-\$	-\$	-\$	-\$	-\$
Decrease MBS cost offset by 20%	-\$	-\$	-\$	-\$	-\$
Assume no BMD monitoring with TDF ⁵	-\$	-\$	-\$	-\$	-\$

¹Assume a DPMQ for each TAF and TDF service of \$961.64

²Assume 99.86% PBS scripts at copayment of \$25.73 each and 0.14% RPBS scripts at copayment of \$5.54 each

³Assume a MBS cost of \$29.33 for each TDF service and

⁴Calculated by the net cost of TAF script minus the cost offset from switching from TDF and MBS offset for TDF.

⁵Assume \$0 for BMD monitoring, resulting in an expected monitoring cost for TDF of \$20.91 per TDF script

Source: Table E-4, p143, table E-5, p144, table E-4, p145 and table E-5, p146 of the submission

6.30 The submission estimated a saving of less than \$10 million to the overall government budget by the fifth year of listing and a total of less than \$10 million over the first five years of listing. This saving was entirely derived from the assumed MBS cost offsets associated with additional clinical monitoring (renal and BMD) for TDF. The evaluation considered that number of BMD tests may be an overestimate and thus the savings would also be overestimated. The ESC and PBAC agreed that the MBS offset was overestimated and unlikely to be realised in practice.

6.31 The PBAC considered that TAF will substitute for entecavir as well as TDF and noted that the financial estimates will need to be recalculated to take this into account.

Quality Use of Medicines

6.32 No quality use of medicine initiatives had been identified by the submission. Given the similarities between TAF and TDF but a difference in dosage, initiatives such as clinician training and patient education may be necessary to minimise confusion.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of tenofovir alafenamide (TAF) as a Section 100 (Highly Specialised Drugs Program – Community Access): Authority Required (STREAMLINED) listing for the treatment of chronic hepatitis B infection (CHB). The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of TAF would be acceptable if it were cost-minimised against entecavir.
- 7.2 The PBAC recommended that the equi-effective doses to be TAF 25 mg once daily is equivalent to entecavir 0.5 mg once daily for nucleos(t)ide naïve CHB patients, and entecavir 1 mg once daily for nucleos(t)ide experienced CHB patients, with the proportions of use of the two entecavir strengths reflecting current usage under the PBS.
- 7.3 The PBAC believed there is a clinical place for TAF as another treatment option alongside TDF and entecavir in the first line treatment of CHB infection, as well as an alternative in cases where the patient has developed resistance to lamivudine.
- 7.4 The PBAC recommended that TAF should not be treated as interchangeable on an individual patient basis with any other drug.
- 7.5 The PBAC advised that TAF is not suitable for prescribing by nurse practitioners as other listings for chronic hepatitis B are currently not included for prescribing by nurse practitioners.
- 7.6 The PBAC recommended that the Early Supply Rule should apply as it applies to other drugs listed under the Section 100 Highly Specialised Drugs Program (Community Access).
- 7.7 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
TENOFOVIR ALAFENAMIDE Tablets, 25mg, 30	2	5	Vemlidy	Gilead Sciences

Category / Program	Section 100 – Highly Specialised Drugs Program – Community Access
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
PBS Indication:	Chronic hepatitis B infection
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required (STREAMLINED)
Clinical criteria:	Patient must have cirrhosis , AND Patient must be nucleoside analogue naive , AND Patient must have detectable HBV DNA, AND The treatment must be the sole PBS-subsidised therapy for this condition.
Prescriber Instructions	Patients with Child's class B or C cirrhosis (ascites, variceal bleeding, encephalopathy, albumin less than 30 g per L, bilirubin greater than 30 micromoles per L) should have their treatment discussed with a transplant unit prior to initiating therapy.
Administrative Advice	Patients may receive treatment in combination with lamivudine but not with other PBS-subsidised antihepadnaviral therapy.

Category / Program	Section 100 (Highly Specialised Drug) Community Access
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
PBS Indication:	Chronic hepatitis B infection
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required (STREAMLINED)
Clinical criteria:	Patient must not have cirrhosis , AND Patient must be nucleoside analogue naive , AND Patient must have elevated HBV DNA levels greater than 20,000 IU/mL (100,000 copies/mL) if HBeAg positive, in conjunction with documented hepatitis B infection; OR Patient must have elevated HBV DNA levels greater than 2,000 IU/mL (10,000 copies/mL) if HBeAg negative, in conjunction with documented hepatitis B infection, AND Patient must have evidence of chronic liver injury determined by: (i) confirmed elevated serum ALT; or (ii) liver biopsy, AND The treatment must be the sole PBS-subsidised therapy for this condition.
Notes:	Patients may receive treatment in combination with lamivudine but not with other PBS-subsidised antihepadnaviral therapy.

Category / Program	Section 100 (Highly Specialised Drug) Community Access
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
PBS Indication:	Chronic hepatitis B infection
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required (STREAMLINED)
Clinical criteria:	Patient must have cirrhosis , AND Patient must have failed antihepadnaviral therapy , AND Patient must have detectable HBV DNA.
Prescriber instructions	Patients with Child's class B or C cirrhosis (ascites, variceal bleeding, encephalopathy, albumin less than 30 g per L, bilirubin greater than 30 micromoles per L) should have their treatment discussed with a transplant unit prior to initiating therapy.
Notes:	Patients may receive treatment in combination with lamivudine but not with other PBS-subsidised antihepadnaviral therapy.

Category / Program	Section 100 (Highly Specialised Drug) Community Access authority required (STREAMLINED)
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
PBS Indication:	Chronic hepatitis B infection
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required (STREAMLINED)
Clinical criteria:	Patient must not have cirrhosis , AND Patient must have failed antihepadnaviral therapy , AND Patient must have repeatedly elevated serum ALT levels while on concurrent antihepadnaviral therapy of greater than or equal to 6 months duration, in conjunction with documented chronic hepatitis B infection; OR Patient must have repeatedly elevated HBV DNA levels one log greater than the nadir value or failure to achieve a 1 log reduction in HBV DNA within 3 months whilst on previous antihepadnaviral therapy, except in patients with evidence of poor compliance.
Notes:	Patients may receive treatment in combination with lamivudine but not with other PBS-subsidised antihepadnaviral therapy.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

The sponsor had no comment.