5.01 DOLUTEGRAVIR with LAMIVUDINE, Tablet containing dolutegravir 50 mg (as sodium) with lamivudine 300 mg, Dovato®, ViiV Health Care Pty Ltd.

For improved readability, this Public Summary Document (PSD) uses tradenames for fixed dose combination (FDC) therapies for the treatment of human immunodeficiency virus (HIV). Table 1 presents a summary of the FDCs, indicating their components, abbreviations for each drug and their associated tradenames. Use of the term "DTG + 3TC" in this document refers to use of a concomitant regimen of dolutegravir and lamivudine, as used in the key effectiveness trials (GEMINI-1/GEMINI-2).

Table 1: Summary of fixed dose combinations (their components, abbreviations for each drug and their associated tradenames)

Fixed dose combination (FDC) components	Abbreviations	Tradename
Dolutegravir/lamivudine	DTG/3TC	Dovato®
Dolutegravir/rilpivirine	DTG/RPV	Juluca®
Elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine	ELV/c/TAF/FTC	Genvoya®
Elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine	ELV/c/TDF/FTC	Stribild®
Rilpivirine/tenofovir alafenamide/emtricitabine	RPV/TAF/FTC	Odefsey®
Rilpivirine/tenofovir disoproxil fumarate/emtricitabine	RPV/TDF/FTC	Eviplera®
Dolutegravir/abacavir/lamivudine	DTG/ABC/3TC	Triumeq®
Bictegravir/tenofovir alafenamide/emtricitabine	BIC/TAF/FTC	Biktarvy®
Efavirenz/tenofovir disoproxil fumarate/emtricitabine	EFV/TDF/FTC	Atripla®
Tenofovir disoproxil fumarate/emtricitabine	TDF/FTC	Truvada®
Tenofovir alafenamide/emtricitabine	TAF/FTC	Descovy®

1 Purpose of Application

1.1 The submission requested a Section 100 (Highly Specialised Drugs Program – Community Access), streamlined authority listing for dolutegravir/lamivudine (DTG/3TC, Dovato®) fixed dose combination (FDC) tablet for the treatment of HIV in adult and adolescent patients.

1.2 The basis of the requested listing was on a cost-minimisation basis compared with the individual components in the FDC (DTG and 3TC).

1.3 Table 2 presents the key components of the clinical issue addressed by the submission.

Table 2: Key components of the clinical issue addressed by the submission

Component	Description
Population	Treatment of HIV infection in adults and adolescents from 12 years of age
Intervention	Dolutegravir 50mg/lamivudine 300mg (DTG/3TC) fixed dose combination (FDC); Dovato®
Comparator	1) Individual components (dolutegravir 50mg and lamivudine 300mg) taken concomitantly 2) Therapies prescribers would most likely replace in practice*
Outcomes	HIV-1 RNA <50 copies at Week 48; FDA snapshot at 48 weeks
Clinical claim	Bioequivalence: Dolutegravir / lamivudine bilayer FDC is an acceptable pharmacokinetic bridge to co-administration of the individual components (DTG + 3TC). Efficacy: Dolutegravir / lamivudine is non-inferior in terms of comparative effectiveness to Biktarvy®, Genvoya®, Stribild®, Odefsey®, Eviplera® and Triumeq® for the treatment of HIV infection. *There is no direct evidence presented in the submission to support this claim.* Safety: TDF regimens (Stribild®, Eviplera®) are inferior in terms of safety to non-TDF regimens (Dovato®, Triumeq®, Biktarvy®, Genvoya®, Odefsey®) for the treatment of HIV infection.

Source: Table 3, p15 of the submission.
FDC = fixed dose combination; HIV = human immunodeficiency virus; mg = milligram; RNA = ribonucleic acid, TDF = tenofovir disoproxil fumarate

* three-drug FDCs currently listed on the PBS (Biktarvy®, Genvoya®, Stribild®, Odefsey®, Eviplera® and Triumeq®) for the treatment of treatment-naïve and -experienced patients with HIV infection

2 Requested listing

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
Dolutegravir 50mg (as sodium) with lamivudine 300mg, tablets, 30	*2*	*60*	*5*	*$[redacted]*	*Dovato® , ViiV Health care Pty Ltd.*

Episodicity:	Daily, continuous treatment
Condition:	HIV infection
PBS Indication:	HIV infection
Treatment phase:	Initial
Restriction:	☐ Restricted benefit ☐ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☒ Streamlined
Clinical criteria:	Patient must be antiretroviral treatment naïve
Population criteria:	Patient must be aged 12 years or older AND Patient must weigh 40kg or more

Episodicity:	Daily, continuous treatment
Condition:	HIV infection
PBS Indication:	HIV infection
Treatment phase:	Continuing
Restriction:	☐ Restricted benefit ☐ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☒ Streamlined
Clinical criteria:	Patient must have previously received PBS-subsidised therapy for HIV infection

Population criteria:	Patient must be aged 12 years or older AND Patient must weigh 40kg or more

Source: Table 21-23, pp39-40 of the submission.

2.1 No details of any Special Pricing Arrangement were presented.

2.2 The restriction included treatment-experienced patients, which was inconsistent with the population in the GEMINI trials and the indication recommended by the TGA evaluator (round 1 and round 2).

3 Background

Registration status

3.1 The submission was made under TGA/PBAC Parallel Process. TGA status at time of PBAC consideration: The Delegate's Request for ACM Advice became available prior to consideration. The Delegate remained of the view the risk-benefit profile of Dovato was positive in the treatment-naïve population and requested the ACM provide advice on whether registration should include the treatment-experienced population.

4 Population and disease

4.1 The proposed place in therapy of Dovato® is in treatment-naïve and treatment-experienced HIV-1 patients. The proposed population includes treatment-naïve individuals as well as patients who would switch treatment (treatment-experienced), while the pivotal GEMINI trials only included treatment-naïve patients. The TGA clinical evaluator's reports and Delegate's Overview recommended an indication for only treatment-naïve patients, though the sponsor presented several arguments for including treatment-experienced patients.

4.2 HIV is an enveloped single-stranded RNA retrovirus that attaches to CD4 receptors expressed on the surface of lymphocytes, destroying or impairing the function of the immune system.

4.3 If left untreated, patients experience a gradual decline in CD4 cell count, with a median loss of 80 cells/mm^3 per year. Progression to Acquired Immunodeficiency Syndrome (AIDS), marked by the development of opportunistic infections or specific malignancies, occurs a median of 10 years after initial infection with HIV. At this time, CD4 cell count usually falls below 200 cells/mm^3 and patients are severely immunocompromised (ASHM 2015).

4.4 The proportion of patients living with diagnosed HIV aged over 50 years has increased (44% in 2015 to 46% in 2017), correlating with the improved survival through the availability of anti-retroviral therapy (ART) and a reduction in AIDS-related complications.

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

5 Comparator

5.1 The submission nominated the component products dolutegravir 50mg and lamivudine 300mg, taken concomitantly (DTG + 3TC), as a comparator. The main arguments provided in support of this nomination were recommendations from the PBAC guidelines (Version 5, Section P1.1.1, p126). The submission noted that pricing based on the individual components was utilised in the cost-minimisation analyses to determine the lowest cost iteration of Dovato®. A bioequivalence study supported this cost-minimisation approach.

5.2 The submission also nominated several single tablet three-drug regimens that prescribers would most replace in practice if use were expected to vary from the current concomitant use of the individual components: Genvoya®, Stribild®, Odefsey®, Eviplera®, Triumeq®, and Biktarvy®, addressing the requirement to consider therapies that would most likely be replaced in practice. Single tablet regimens excluded as comparators by the submission included Atripla® and Juluca®. The PBAC previously advised it was of the view that therapies containing efavirenz (i.e. Atripla) are of inferior safety to non-efavirenz containing therapies for the treatment of HIV infection (dolutegravir/rilpivirine Public Summary Document July 2018, paragraph 7.8).

5.3 The PBAC guidelines do not limit the consideration of most replaced therapies in practice to other single tablet fixed dose combination regimens and could include multi-tablet regimens. Notably, the comparator in the pivotal GEMINI trials was a multi-drug regimen of dolutegravir (DTG) + a tenofovir disoproxil fumarate/ emtricitabine FDC (Truvada®). This drug combination was not included in the cost-minimisation and the submission did not explicitly address the relativities of the comparator in the GEMINI trials to the nominated single tablet three-drug FDC comparators in its clinical claim. DTG + Truvada® is also more costly than the requested price for Dovato®.

5.4 For the requested population, and among the therapies nominated as relevant comparators by the submission, none of the alternative therapies are less costly than the requested price for Dovato®, based on PBS prices current in May 2019. Other multi-drug treatment combinations for the treatment of HIV infection that could be considered as alternatives could be less costly than Dovato®. If treatment with Dovato® is substantially more costly than an alternative therapy or alternative therapies, the PBAC could only recommend listing of Dovato® if it is satisfied the FDC provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies (*National Health Act 1953*, Section 101(3B)).

5.5 Technically, Dovato®, as two-drug regimen and a departure from established three-drug regimens, may not constitute a recommended regimen for most patients initiating HIV treatment. The ESC considered the introduction of two-drug regimens as standard therapy might represent a substantial change in approach to the treatment of HIV infection. Such a shift may have acceptability issues in the Australian

context given a substantial number of people living with HIV are older and have lived with HIV for long periods following the introduction of ARTs.

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 presenting clinician highlighted that management of HIV is now a relatively straightforward and established process in clinical practice and while three drug regimens (3DR) are the current standard, evidence for effective two drug regimens (2DR) is emerging, such as dolutegravir/rilpivirine (Juluca®) for virologically-suppressed treatment experienced patients and in Europe, boosted protease inhibitor-only regimens. The clinician highlighted that as the prevalent HIV population continues to age, new medical challenges are starting to emerge such as comorbidities and drug interactions from polypharmacy, which may make effective 2DRs more desirable and acceptable for some virologically suppressed patients.

Consumer comments

6.2 The PBAC noted the advice from Positive Life NSW, which supported the listing of a two-drug regimen as it may improve medication management and adherence for some people living with HIV, especially those who are managing multiple health conditions.

Clinical trials

6.3 The submission was based on:

- two identical randomised trials (GEMINI-1: N=719; GEMINI-2: N=722) comparing concomitant dolutegravir + lamivudine (DTG + 3TC) to dolutegravir + tenofovir disoproxil fumarate/emtricitabine FDC (DTG + TDF/FTC or DTG + Truvada®) in treatment-naïve patients with HIV-1 infection;
- one open-label, single dose, randomised, two-part, pivotal bioequivalence crossover study (Study 204994: Part 1 N=78; Part 2 N=76) of two formulations of a fixed dose combination of DTG/3TC (Part 1: monolayer tablet formulation; Part 2: bilayer tablet formulation) relative to the co-administration of the single entity products (DTG + 3TC) in healthy adult subjects aged 18-55 years; and
- several supplementary non-randomised studies investigating the effectiveness or safety of DTG + 3TC taken concomitantly.

6.4 The submission also presented interim results (24 weeks) of the TANGO trial (N=743) comparing Dovato® to continuation of a tenofovir alafenamide (TAF) based regimen in virologically suppressed patients with uninterrupted TAF based regimen for at least

6 months prior to screening with no evidence or history of ART drug resistance. The submission stressed that the interim analyses have been provided in confidence and complete redaction from any publicly available documentation would be necessary prior to publication of the results.

6.5 Details of the trials and studies presented in the submission are provided in Table 3.

Table 3: Trials and studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
GEMINI-1 / GEMINI-2	Study 204861 (GEMINI-1): A Phase III, randomized, double-blind, multicentre, parallel-group, non-inferiority study evaluating the efficacy, safety, and tolerability of dolutegravir plus lamivudine compared to dolutegravir plus tenofovir/emtricitabine in HIV-1 infected treatment naïve adults – Week 48.	CSR. 05 September 2018
	Study 205543 (GEMINI-2): A Phase III, randomized, double-blind, multicentre, parallel-group, non-inferiority study evaluating the efficacy, safety, and tolerability of dolutegravir plus lamivudine compared to dolutegravir plus tenofovir/emtricitabine in HIV-1 infected treatment-naïve adults – Week 48	CSR. 05 September 2018
	Module 5.3.5.3: Integrated Summary of Efficacy, Integrated Summary of Safety. 2018	2018. Internal Report
	Cahn P, Sierra Madero J, Arribas JR, et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials.	Lancet 2018; Published online: November 9, 2018. http://dx.doi.org/10.1016/ S0140-6736(18)32462-0
	Cahn, P., Sierra Madero, J., Arribas, J., et al. Non-inferior efficacy of dolutegravir (DTG) plus lamivudine (3TC) vs DTG plus tenofovir/emtricitabine (TDF/FTC) fixed-dose combination in antiretroviral treatment–naive adults with HIV-1 infection—Week 48 results from the GEMINI studies.	22nd International AIDS Conference; 2018
TANGO	A Phase III, randomized, multicenter, parallel-group, noninferiority study evaluating the efficacy, safety, and tolerability of switching to dolutegravir plus lamivudine in HIV 1 infected adults who are virologically suppressed	Protocol: 29 August 2018
Bioequivalence Study		
Study 204994	An Open-Label, Randomized, Single dose, Crossover, Pivotal Bioequivalence Study of Fixed-dose Combination Tablet(s) of Dolutegravir and Lamivudine versus Dolutegravir and Lamivudine single entities and Food Effect Assessment in Healthy Volunteers.24	CSR May 2018
Supportive evidence: additional prospective and observational studies		
PADDLE	Cahn P, Rolon MJ, Figueroa MI, et al. Dolutegravir-lamivudine as initial therapy in HIV-1 infected, ARV-naive patients, 48-week results of the PADDLE (Pilot Antiretroviral Design with Dolutegravir Lamivudine) study.	Journal of the International AIDS Society 2017; 20(1):21678
	Cahn P, Rolon MJ, Figueroa MI, et al. Dolutegravir-lamivudine as initial therapy in HIV-infected, ARV naive patients: 48 week results of the PADDLE trial.	21st International AIDS Conferences; 2016
	Figueroa, M. I. Dolutegravir-Lamivudine as initial therapy in HIV-1 infected, ARV-naive patients: 96 week results of the PADDLE trial.	9th IAS Conference on HIV Science; 2017
ACTGA5353	Taiwo BO, Zheng L, Stefanescu A, et al. ACTG A5353: A pilot study of dolutegravir plus lamivudine for initial treatment of HIV-1-infected participants with HIV-1 RNA < 500,000 copies/mL	Clinical Infectious Diseases. 2018; 66(11):1689-97.

Trial ID	Protocol title/ Publication title	Publication citation
	Taiwo BO, Zheng, L, Nyaku AN, et al. ACTG A5353: A pilot study of dolutegravir (DTG) + lamivudine (3TC) for initial treatment of HIV-1-infected participants with HIV-1 RNA < 500,000 copies/mL.	9th IAS Conference on HIV Science; 2017
ASPIRE	Taiwo BO, Marconi VC, Berzins B, et al. Dolutegravir plus lamivudine maintain HIV-1 suppression through week 48 in a pilot randomized trial.	Clinical Infection Diseases. 2018b; 66(11):1794-1797
	Taiwo BO, Marconi V, Berzins B, et al. Dolutegravir plus lamivudine maintains HIV-1 suppression in plasma and genital secretions through week 24 in a pilot randomized trial.	9th IAS Conference on HIV Science; 2017;
LAMIDOL	Joly V, Burdet C, Landman R, et al. Dolutegravir and lamivudine maintenance therapy in HIV-1 virologically suppressed patients: results of the ANRS 167 trial (LAMIDOL).	The Journal of Antimicrobial Chemotherapy. 2018; Nov 23. doi: 10.1093/jac/dky467
	Joly V, Burdet C, Landman R, et al. Promising results of lamivudine + dolutegravir maintenance therapy in ANRS 167 Lamidol trial.	Conference on Retroviruses and Opportunistic Infections (CROI) 2017; 2017
	Joly V, Burdet C, Raffi F, et al. Promising results of dolutegravir + lamivudine maintenance in ANRS167 LAMIDOL trial.	16th European AIDS Conference; 2017
Borghetti 2016	Borghetti A, Baldin G, Ciccullo A, et al. Virological control and metabolic improvement in HIV-infected, virologically suppressed patients switching to lamivudine/dolutegravir dual therapy.	The Journal of Antimicrobial Chemotherapy. 2016;71(8):2359-2361
Baldin 2016	Baldin G, Borghetti A, Capetti A, et al. Efficacy and safety of lamivudine-dolutegravir in a multicenter cohort of HIV-infected, virologically suppressed patients.	Italian Conference on AIDS and Antiviral Research (ICAR) 2016;
Borghetti 2017	Borghetti A, Moschese D, Baldin G, et al. Efficacy and tolerability of lamivudine plus dolutegravir compared with lamivudine plus boosted PLS in HIV-positive, virologically-suppressed individuals from the clinical practice.	16th European AIDS Conference; 2017
	Borghetti A, Moschese D, Baldin G, et al. A 48 week comparison of immunological, metabolic and renal function changes in a cohort of HIV+, virologically suppressed patients switching to lamivudine plus either darunavir/ritonavir, atazanavir/ritonavir or dolutegravir.	16th European AIDS Conference; 2017
Ciccullo 2018	Ciccullo A, Baldin G, Capetti A., et al. A comparison between two dolutegravir-based two-drug regimens as switch strategies in a multicentre cohort of HIV-1-infected patients	Antiviral Therapy. 2018
Cucchetto 2016	Cucchetto G, Lanzafame M, Nicole S, et al. Integrase inhibitors with lamivudine, as maintenance-dual therapy, in a real-life clinical setting.	Italian Conference on AIDS and Antiviral Research (ICAR) 2016
Hidalgo-Tenorio 2017	Hidalgo-Tenorio C, De Jesus SE, Santos J, et al. Multicenter study of the effectiveness and safety of a dual therapy with dolutegravir plus lamivudine in treatment-experienced HIV patients.	16th European AIDS Conference; 2017
Yagci Caglayik 2017	Yagci Caglayik, D., Gokengin, D., Inan, A., et al. Real life experience of dolutegravir and lamivudine dual therapy as a switching regimen in HIV-TR Cohort.	16th European AIDS Conference; 2017
Borghetti 2018	Borghetti A, Baldin G, Lombardi F, et al. Efficacy and tolerability of lamivudine plus dolutegravir as a switch strategy in a multicentre cohort of patients with suppressed HIV-1 replication.	HIV Medicine. 2018;19 (7) 452-454
Maggiolo 2017	Maggiolo F, Gulminetti R, Pagnucco L, et al. Lamivudine/dolutegravir dual therapy in HIV-infected, virologically suppressed patients.	BMC Infectious Diseases. 2017a;17(1):215
	Maggiolo F, Gulminetti R, Pagnucco L, et al. Durability of dolutegravir + lamivudine as simplification cART in patients with suppressed HIV-RNA.	Presented at: 16th European AIDS Conference; October 25-27, 2017b; Milan, Italy.
	Maggiolo F, Gulminetti R, Pagnucco L, Lamivudine+dolutegravir as simplification strategy in patients with suppressed HIV RNA.	Journal of the International AIDS Society,2016

Trial ID	Protocol title/ Publication title	Publication citation
Tan 2018	Tan M, Johnston S, Nicholls J, et al. Dual therapy with dolutegravir and renally adjusted lamivudine in HIV infection: A treatment strategy to manage comorbidity and toxicity in older patients.	HIV Medicine, 2018; 19, S24.
DOLULAM	Reynes J, Meftah N, Montes B. Dual regimen with dolutegravir and lamivudine maintains virologic suppression even in heavily treatment-experienced HIV-infected patients: 48-week results from a pilot study (DOLULAM).	Journal of the International AIDS Society. 2016;19(Suppl 7):68-69.
	Reynes J, Meftah N, Tuaillon E, et al. Dual regimen with dolutegravir and lamivudine maintains virologic suppression even in heavily treatment experienced HIV-infected patients: 96 weeks results from maintenance DOLULAM study.	9th IAS Conference on HIV Science (IAS 2017)
DOLAM	Blanco JL, Rojas J, Paredes R, et al. Dolutegravir-based maintenance monotherapy versus dual therapy with lamivudine: A planned 24 week analysis of the DOLAM randomized clinical trial.	Journal of Antimicrobial Chemotherapy, 2018; 73, 1965-1971.

Source: Table 27, pp45-57 of the submission.

6.6 The key features of the direct randomised trials are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
DTG + 3TC versus DTG + Truvada®					
GEMINI 1	719	R, DB 48 weeks*	Low	Treatment naïve	HIV-1 RNA <50 copies at Week 48; FDA snapshot at 48 weeks
GEMINI 2	722				
Dovato® versus tenofovir alafenamide based regimen (TBR)					
TANGO	743	R, OL 24 weeks*	Unknown /high	Treatment experienced	HIV-1 RNA <50 copies at Week 24; FDA snapshot at 24 weeks
Dovato® versus DTG + 3TC					
Study 204994	Part 1, n=78	SC, OL, R SD, C/O	Low	Healthy subjects; 18-55 years; ≥50kg (men) or ≥45kg (women); BMI: 18-31.0 kg/m^2	Demonstration of bioequivalence
	Part 2, n=76				

Source: Table 29, p48, Table 58, p83, and pp147-151 of the submission.
C/O = crossover; DB=double blind; MC=multi-centre; NA = not applicable; OL=open label; R=randomised.SC = single centre; SD = single dose

6.7 The GEMINI trials and Study 204994 were considered to be of low risk of bias. The TANGO trial appeared to have generally unknown or high risk of bias. Though the randomisation appears to have been adequately carried out, the trial was open-label and no information could be found to assess attrition or other biases. No CSR was available which increases the risk of reporting bias. On clinicaltrials.gov, the primary completion date for the TANGO trial was June 2019.

6.8 The safety claim that TDF regimens (Stribild®, Eviplera®) are inferior in terms of safety to non-TDF regimens (Dovato®, Triumeq®, Biktarvy®, Genvoya®, Odefsey®) for the treatment of HIV infection, was primarily based on several observational studies. The quality of the evidence and process by which the claim of inferior safety associated with TDF regimens presented in the submission is not as robust as what is typically presented in superior safety claims (i.e. direct trial evidence or indirect comparisons).

Comparative effectiveness

6.9 Overall, similar rates of virological response were observed across the treatment arms, as were similar proportions of patients meeting confirmed virological withdrawal criteria.

6.10 Table 5 presents results of the comparison of HIV -1 RNA <50 copies at Week 48 in the GEMINI 1 and 2 trials.

Table 5: Proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Week 48 – snapshot analyses

Trial	n/N (%)		RD, % (95% CI)	
	DTG + 3TC	DTG + Truvada®	Unadjusted^	Adjusted*
ITT-E population: Primary dataset				
GEMINI-1	320/356 (89.9)	332/358 (92.7)	-2.8 (-7.0, 1.3)	-2.6 (-6.7, 1.5)
GEMINI-2	335/360 (93.1)	337/359 (93.9)	-0.8 (-4.4, 2.8)	-0.7 (-4.3, 2.9)
Pooled	655/716 (91.5)	669/717 (93.3)	-1.8 (-4.6, 0.9)	-1.7 (-4.4, 1.1)
PP population				
GEMINI-1	317/345 (91.9)	325/346 (93.9)	-2.0 (-5.9, 1.8)	-1.9 (-5.7, 1.9)
GEMINI-2	328/349 (94.0)	329/347 (94.8)	-0.8 (-4.2, 2.6)	-0.7 (-4.1, 2.7)
Pooled	645/694 (92.9)	654/693 (94.4)	-1.4 (-4.0, 1.1)	-1.3 (-3.9, 1.2)
ITT population				
GEMINI-1	320/359 (89.1)	332/360 (92.2)	-3.1 (-7.3, 1.2)	-2.9 (-7.1, 1.3)
GEMINI-2	335/360 (93.0)	337/362 (93.0)	0.0 (-3.7, 3.7)	0.1 (-3.6, 3.8)
Pooled	655/719 (91.0)	669/722 (92.6)	-1.6 (-4.4, 1.3)	-1.4 (-4.2, 1.4)

Source: Table 38, p61 of the submission.

3TC = lamivudine; CI = confidence interval; DTG = dolutegravir; ITT = intent to treat; ITT-E = intent to treat exposed; PP = per protocol; RD = risk difference.

^ Difference: Proportion for DTG + 3TC – Proportion for DTG + Truvada®

* Adjusted: Based on CMH-stratified analysis adjusted for the following baseline stratification factors: Plasma HIV-1 RNA (≤100,000 copies/mL vs >100,000 copies/mL and CD4+ count (≤200 cells/mm^3 vs >200 cells/mm^3). Pooled analysis also stratified by study (GEMINI-1, GEMINI-2)

6.11 The results fell within the nominated non-inferiority margin of -10%.

6.12 Table 6 presents the FDA snapshot analysis at 48 weeks of the GEMINI 1 and 2 trials.

Table 6: Snapshot analysis at 48 weeks (ITT-E Population)

n (%)	GEMINI-1		GEMINI-2		Pooled	
	DTG + 3TC	DTG + Truvada®	DTG + 3TC	DTG + Truvada®	DTG + 3TC	DTG + Truvada®
	(N=356)	(N=358)	(N=360)	(N=359)	(N=716)	(N=717)
HIV-1 RNA <50 c/mL	320 (89.9)	332 (92.7)	335 (93.1)	337 (93.9)	655 (91.5)	669 (93.3)
HIV-1 RNA ≥50 c/mL	13 (3.7)	6 (1.7)	7 (1.9)	7 (1.9)	20 (2.8)	13 (1.8)
Data in window & HIV-1 RNA ≥50c/mL	6 (1.7)	3 (0.8)	2 (0.6)	2 (0.6)	8 (1.1)	5 (0.7)
Disc: lack of efficacy	3 (0.8)	1 (0.3)	2 (0.6)	1 (0.3)	5 (0.7)	2 (0.3)
Disc: other reason & HIV-1 RNA >50c/mL	3 (0.8)	2 (0.6)	2 (0.6)	3 (0.8)	5 (0.7)	5 (0.7)
Change in ART	1 (0.3)	0	1 (0.3)	1 (0.3)	2 (0.3)	1 (0.1)
No virological data at Week 48	23 (6.5)	20 (5.6)	18 (5.0)	15 (4.2)	41 (5.7)	35 (4.9)
Disc trial due to AE/Death	5 (1.4)	9 (2.5)	5 (1.4)	4 (1.1)	10 (1.4)	13 (1.8)
Disc trial for other reasons	17 (4.8)	11 (3.1)	12 (3.3)	11 (3.1)	29 (4.1)	22 (3.1)
On trial but missing data in window	1 (0.3)	0	1 (0.3)	0	2 (0.3)	0

Source: Table 39, p62 of the submission.
3TC = lamivudine; AE = adverse event; ART = antiretroviral treatment; Disc = discontinued; DTG = dolutegravir; HIV = human immunodeficiency virus; RNA = ribonucleic acid; CI = confidence interval; n = number of participants reporting data; N = total participants in group

6.13 A slightly smaller proportion of patients in the pooled DTG + 3TC arm had HIV-1 RNA <50 copies/mL than in the DTG + Truvada® arm. Otherwise, the snapshot analysis indicated similarity across the two pooled treatment arms.

6.14 Confirmed Virologic Withdrawal (CVW) in the GEMINI trials is presented in Table 7. The CVW criteria were as follows: A second and consecutive HIV-1 RNA value (two to four weeks after initial measurement) meeting virologic non-response or rebound:

- Virologic non-response: a decrease in plasma HIV-1 RNA of less than 1 $\log_{10}$ copies/mL by week 12, unless plasma HIV-1 RNA is <200 copies/mL or confirmed plasma HIV-1 RNA levels ≥200 copies/mL on or after week 24.
- Virological rebound: confirmed rebound in plasma HIV-1 RNA levels to ≥200 copies/mL after prior confirmed suppression to <200 copies/ml.

Table 7: Confirmed virologic withdrawal (ITT-E population)

Time point; n (%)	GEMINI-1		GEMINI-2		Pooled	
	DTG + 3TC (N=356)	DTG + Truvada® (N=358)	DTG + 3TC (N=360)	DTG + Truvada® (N=359)	DTG + 3TC (N=716)	DTG + Truvada® (N=717)
Week 16	1 (0.3)	0	0	0	1 (0.1)	0
Week 24	3 (0.8)	1 (0.3)	2 (0.6)	2 (0.6)	5 (0.7)	3 (0.4)
Week 36	3 (0.8)	1 (0.3)	2 (0.6)	2 (0.6)	5 (0.7)	3 (0.4)
Week 48	4 (1.1)	2 (0.6)	2 (0.6)	2 (0.6)	6 (0.8)	4 (0.6)

Source: Table 40, p62 of the submission. 3TC = lamivudine; DTG = dolutegravir; FTC = emtricitabine; TDF = tenofovir disoproxil fumarate.

6.15 Though no apparent differences were observed in patients with CVW between the treatment arms, it should be noted that results of this outcome were only available up to 48 weeks. Given the two-drug nature of the proposed regimen is a substantial

departure from established three-drug treatment, results from a longer duration of follow-up would be highly informative. The ESC considered the introduction of 2-drug regimens as standard therapy represented a potential change from longstanding treatment practice, and that longer-term data on effectiveness and safety would be informative.

6.16 No meaningful differences in change in EQ-5D were observed between the DTG + 3TC and DTG + Truvada® in the GEMINI trials at 48 weeks.

6.17 Tables 8 and 9 present preliminary results of the TANGO trial.

Table 8: Results for proportion of subjects with HIV-1 RNA <50 copies/mL at week 24, TANGO (ITT-E population)

Treatment arm	Events,-n/N (%)	RD% (95% CI)	
		Unadjusted	Adjusted*
Dovato®	350/369 (95%)	[redacted]	-1.4 (-4.4, 1.6)
Tenofovir alafenamide based regimen (TBR)	358/372 (96%)		

Source: Table 115, p151 of the submission.
RD = risk difference; TBR = tenofovir alafenamide based regimen
* Adjusted: based on Cochran-Mantel Haenszel test stratified by baseline third agent class (PI, INI, or NNRTI)

Table 9: **Snapshot analysis at 24 weeks TANGO (ITT-E)**

	Dovato® (N=369)	TBR (N=372)
HIV-1 RNA <50 c/mL	350 (95)	358 (96)
HIV-1 RNA ≥50 c/mL	1 (<1)	3 (<1)
Data in window & HIV-1 RNA ≥50c/mL	[redacted]	[redacted]
Discontinued for lack of efficacy	[redacted]	[redacted]
Discontinued for other reason and HIV-1 RNA ≥50 copies/mL	[redacted]	[redacted]
Change in ART	[redacted]	[redacted]
No virological data at Week 48	18 (5)	11 (3)
Discontinued trial due to AE/Death	[redacted]	[redacted]
Discontinued trial for other reasons	[redacted]	[redacted]
On trial but missing data in window	[redacted]	[redacted]

Source: Table 116, p151 of the submission.
AE = adverse event; ART = antiretroviral treatment; Dovato® = dolutegravir/ lamivudine; HIV = human immunodeficiency virus; mL = millilitre; RNA = ribonucleic acid; TBR = tenofovir alafenamide based regimen

6.18 While the TANGO data suggested similar virological response, the analyses at 24 weeks was a short follow-up, and the TANGO trial, as presented, had an uncertain risk of bias.

6.19 The submission presented results of the 204994 bioequivalence study to support the claim that Dovato® provides an acceptable pharmacokinetic bridge to co-administration of the individual components. The TGA clinical evaluator (pp25-26 of CER [first round]) concluded that:

- "The conduct of the single study that was provided in support of the current submission was satisfactory, the data analyses undertaken were appropriate and the analytical methods used to measure exposure levels were validated.

- The proposed bilayer FDC tablet formulation and the free combination were bioequivalent under fasted conditions in regards to the $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$ and Cmax of DTG and the $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$[1] of 3TC. Moreover, the difference in 3TC Cmax following administration of the free combination verses the bilayer FDC is relatively modest and is unlikely to be of clinical significance.
- A high fat meal resulted in a modest increase (approximately 32%) in DTG $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$ and in a modest decrease in 3TC Cmax of approximately 30%.

6.20 The Pre-Sub-Committee Response (PSCR) and Pre-PBAC Response presented an FDA Snapshot analysis for the GEMINI I and II (and pooled) results at 96 weeks and are presented in the table below. The updated analyses were not independently evaluated.

Table 10: FDA 96-week snapshot analysis of GEMINI I, GEMINI II and pooled dataset

96-week analyses; n (%)	GEMINI-1		GEMINI-2		Pooled	
	DTG + 3TC	DTG + TDF/FTC	DTG + 3TC	DTG + TDF/FTC	DTG + 3TC	DTG + TDF/FTC
	(N=356)	(N=358)	(N=360)	(N=359)	(N=716)	(N=717)
HIV-1 RNA <50 c/mL	300 (84.2)	320 (89.4)	316 (87.8)	322 (89.7)	616 (86.0)	642 (89.5)
Adjusted RD% (95% CI)	-4.9 (-9.8, 0.0)		-1.8 (-6.4, 2.7)		-3.4 (-6.7, 0.0)	
HIV-1 RNA ≥50 c/mL	[redacted]				22 (3.1)	14 (2.0)
Data in window & HIV-1 RNA ≥50c/mL						
Disc: lack of efficacy						
Disc: other reason & HIV-1 RNA >50c/mL						
Change in ART						
No virological data					78 (10.9)	61 (8.5)
Disc trial due to AE/Death					22 (3.1)	21 (2.9)
Disc trial for other reasons					56 (7.8)	38 (5.3)
On trial but missing data in window					0	2 (0.3)
CVW at week 96	5 (1.4)	4 (1.1)	6 (1.7)	3 (0.8)	11 (1.5)	7 (1.0)

Source: Pre-PBAC Response (Table 3).

6.21 In the updated analyses, the lower bound of the 95% CI for adjusted risk difference for HIV-1 RNA of less than 50 copies per mL remained within the pre-specified non-inferiority margin of -10% for both studies and the pooled analysis.

Comparative harms

6.22 Table 11 presents a summary of adverse events in the GEMINI 1 and 2 trials.

[1] $AUC_{0\text{-}inf}$: Area under the plasma concentration time curve from zero to infinity
$AUC_{0\text{-}t}$: Area under the plasma concentration time curve from zero to the last quantifiable time point
Cmax: maximum observed concentration

Table 11: **Summary of AEs (safety population)**

n (%)	GEMINI-1		GEMINI-2		Pooled			
	DTG + 3TC (N=356)	DTG + Truvada® (N=358)	DTG + 3TC (N=360)	DTG + Truvada® (N=359)	DTG + 3TC (N=716)	DTG + Truvada® (N=717)	RR (95% CI)^	RD% (95% CI)^
Any AE	276 (77.5)	295 (82.4)	267 (74.2)	284 (79.1)	543 (75.8)	579 (80.8)	**0.94 (0.89, 0.99)**	**-4.9 (-9.2, -0.7)**
DR AE	[redacted]	[redacted]	[redacted]	[redacted]	126 (17.6)	169 (23.6)	**0.75 (0.61, 0.92)**	**-6.0 (-10.1, -1.8)**
Grade 2-5 AE	[redacted]	[redacted]	[redacted]	[redacted]	404 (56.4)	425 (59.3)	0.95 (0.87, 1.04)	-2.9 (-8.0, 2.3)
DR grade 2-5 AE	21 (5.9)	25 (7.0)	21 (5.8)	22 (6.1)	42 (5.9)	47 (6.6)	0.89 (0.60, 1.34)	-0.7 (-3.2, 1.8)
AE leading to withdrawal	[redacted]	[redacted]	[redacted]	[redacted]	15 (2.1)	16 (2.2)	1.00 (0.49, 2.03)	-0.1 (-1.6, 1.4)
DR AE leading to withdrawal	[redacted]	[redacted]	[redacted]	[redacted]	6 (0.8)	9 (1.3)	0.67 (0.24, 1.87)	-0.4 (-1.5, 0.6)
Any SAE	[redacted]	[redacted]	[redacted]	[redacted]	50 (7.0)	55 (7.7)	0.91 (0.63, 1.32)	-0.7 (-3.4, 2.0)
DR-SAE	[redacted]	[redacted]	[redacted]	[redacted]	4 (0.6)	4 (0.6)	1.00 (0.25, 3.99)	0.0 (-0.8, 0.8)
Fatal AE	[redacted]	[redacted]	[redacted]	[redacted]	2 (0.3)	0	-	0.3 (-0.1, 0.7)
DR fatal AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 48, p71 of the submission. 3TC = lamivudine; AE = adverse events; CI = confidence interval; DR = drug related; DTG = dolutegravir; FTC = emtricitabine; RD = risk difference; RR = relative risk; SAE = serious adverse event; TDF = tenofovir disoproxil fumarate.
Source: Module 5.3.5.3 – ISS: Table 3; ^Ad-hoc analyses
Bolded values denote statistically significant differences.

6.23 The overall incidence of AEs was slightly lower in the DTG + 3TC compared to the DTG + Truvada® group (76% vs 81%). The most commonly reported AEs were headache, diarrhoea, nasopharyngitis, upper respiratory tract infection (URTI), nausea, insomnia, and pharyngitis. The proportion of subjects reporting events were generally similar across the system organ classes (SOCs) with minor differences observed for some SOCs such as gastro-intestinal disorder, mainly due to higher reporting rate in the DTG + Truvada® group of nausea and diarrhoea. Most of the AEs were Grade 1 (19% vs 21%) or Grade 2 (50% vs 51%) with a similar proportion of subjects reporting any Grade 2-5 AE in the two treatment groups.

6.24 The TGA clinical evaluator considered the safety data from the randomised, double-blind Phase III studies comparing DTG + 3TC to a standard-of-care regimen of DTG + Truvada® was consistent with the known safety profile for the individual products (p60 of CER [round 1]).

6.25 The TGA clinical evaluator noted the "exact number of patients exposed for 6 months and 12 months was not provided. The planned 96 week and 148 week analysis should provide the necessary long-term safety data for proposed combination" (p59 of CER [round 1]).

6.26 The TGA clinical evaluator also noted that patients with suicidality risk were excluded from both pivotal studies (p44 of CER). The Advisory Board Minutes included in Appendix 1 to the submission noted that in the clinical scenario of major depression, DTG was distinct from other INSTIs and that use should trend towards caution.

6.27 The submission also presented results of renal and bone turnover biomarkers as well as lipid parameters. Briefly, the results indicated:

- A statistically significant greater decrease in estimated glomerular filtration rate (GFR) using creatinine-adjusted CKD-EPI equation in the DTG + Truvada® group compared with the DTG + 3TC group (GFR = 3.4ml/min per 1.73m^2, 95% CI: 2.2, 4.5, p<0.001). For estimated GFR using cystatin C-adjusted CKD-EPI equation there was a statistically significant increase in the DTG + 3TC group compared with the DTG + Truvada® group (GFR =2.2ml/min per 1.73m^2, 95% CI: 1.0, 3.4p<0.001). The submission considered that overall, changes in renal biomarkers were generally favourable for DTG + 3TC compared to DTG + Truvada®. For unadjusted serum creatinine outcomes and unadjusted serum Cystatin C outcomes across the GEMINI trials and pooled analyses, confidence intervals crossed zero for most comparisons. Overall, it was difficult to assess the clinical meaningfulness of these results, particularly over a 48 week treatment duration.
- At Week 48 across the pivotal trials and the pooled analysis, all markers of bone turnover assessed increased from baseline in both treatment groups. Significantly larger increases in bone turnover markers were observed in the DTG + Truvada® arm when compared to the DTG + 3TC arm. It was unclear to if, or to what extent, these differences could result in a significant difference in fracture risk between treatment arms.
- In the pooled analysis, changes in LDL, HDL and total cholesterol parameters at Week 48 compared to baseline varied across the treatment arms, with a mean increase observed in the DTG + 3TC arm (LDL: 0.17 mmol/L; HDL: 0.15 mmol/L; total cholesterol: 0.32 mmol/L) and a decrease or marginal differences observed in the DTG + Truvada® arm (LDL: -0.14 mmol/L; HDL: 0.02 mmol/L; total cholesterol: -0.15 mmol/L); adjusted differences between the groups were statistically significant (p<0.001). For total cholesterol/HDL ratio, both treatment groups showed an overall reduction with a greater reduction observed in the DTG + Truvada® arm compared to the DTG + 3TC arm (p=0.018).

6.28 The submission presented a lengthy discussion of safety profiles of various antiretroviral agents, with special importance placed on the safety profile of TDF. This discussion, largely based on observational datasets was used to support a claim that TDF regimens were inferior to non-TDF regimens in terms of safety. The submission's claims regarding bone toxicity did not seem to be supported by the overall evidence. While it appeared that TDF was associated with long term kidney toxicity in multiple long-term observational datasets, the comparative trial of TDF versus TAF regimens presented did not consistently support this claim, nor did the GEMINI trials (versus

DTG + Truvada®). The ESC considered no evidence was presented that supported a difference in safety between a regimen containing TDF (DTG + Truvada) and concomitant dolutegravir + lamivudine (DTG + 3TC) in the GEMINI trials.

Clinical claim

6.29 The submission made the following clinical claims:

- Dovato® is an acceptable pharmacokinetic bridge to co-administration of the individual components (DTG + 3TC). The TGA clinical evaluator (round 1) accepted this claim.
- Dovato® is non-inferior in terms of effectiveness in comparison to Biktarvy®, Genvoya®, Stribild®, Odefsey®, Eviplera® and Triumeq® for the treatment of HIV infection. This relies on the acceptance that the DTG + Truvada® combination assessed in the GEMINI trials could act as a proxy for other three-drug regimens. It should be noted that the included pivotal trial data is only reflective of a treatment-naïve population. The submission considered it reasonable to extrapolate this claim to a treatment switch population on the basis of:

  1) PBAC consideration of Stribild® (Cobicistat + elvitegravir + emtricitabine + tenofovir PSD, March 2013, Section 12 (p5));

  2) Additional observational data and headline results of the TANGO trial.

  The TGA evaluator (round 1) considered that the evidence presented in the TGA dossier did not support an indication that included switch or treatment-experienced patients. The evaluation noted that should this be the case, there would be no grounds to include the treatment-experienced population in a PBS listing. It should also be noted that the GEMINI trials, while largely representative of the Australian population, did appear to have a lower proportion of patients with advanced HIV than the Australian population, and the GEMINI subgroup analyses did indicate a difference in comparative efficacy between treatments in advanced HIV subgroups.
- TDF regimens (Stribild®, Eviplera®) are inferior in terms of safety to non-TDF regimens (Dovato®, Triumeq®, Biktarvy®, Genvoya®, Odefsey®) for the treatment of HIV infection. The submission presented a lengthy discussion of observational data and limited trial data comparing TDF and TAF containing regimens. The submission's claims regarding bone toxicity did not seem to be supported by the overall evidence. While it appeared that TDF was associated with long term kidney toxicity in multiple long-term observational datasets, the comparative trial of TDF versus TAF regimens presented did not consistently support this claim, nor did the GEMINI trials (versus DTG + Truvada®). The submission considered that based on the submission's consideration of extended harms, a claim of inferior safety should be accepted without a trial-based comparison. Alternatively, this claim may be considered a circumvention of a superiority claim on which to base a price premium, which would be based on largely non comparative evidence.

6.30 The Pre-PBAC Response argued there was adequate evidence and precedent to conclude DTG + Truvada could act as a proxy for alternative FDC therapies.

6.31 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable for the treatment-naïve population and deferred consideration of the claim for the treatment-experienced population pending further clarity on the likely final conditions of TGA registration.

6.32 The PBAC considered that the claim of non-inferior comparative safety to non-TDF containing multi-drug regimens was reasonable for the treatment-naïve population and deferred consideration of the claim for the treatment-experienced population pending further clarity on the likely final conditions of TGA registration. The PBAC recalled it had previously advised that claims of 'favourable' comparative safety between TDF and TAF regimens had not been adequately supported (Odefsey® and Descovy® July 2016 Public Summary Documents) and noted no new trial data was presented, and the arguments were based on largely observational evidence. The PBAC remained of the view that it was difficult to discern any clinically meaningful safety advantages between TDF and non-TDF regimens.

6.33 The PBAC recalled when it considered appropriate comparators for Biktarvy at its November 2018 meeting that regimens that contained an unboosted INSTI (rather than a boosted INSTI or NNRTI) were now likely to be used first line in Australian clinical practice. The PBAC recalled its view on the comparative safety profiles of TDF and TAF was not a factor in its recommendation for Biktarvy and re-affirmed its previous opinion expressed in its consideration of Odefsey and Descovy.

Economic analysis

6.34 Table 12 presents the key components and assumptions of the cost-minimisation analysis.

Table 12: **Key components and assumptions of the cost-minimisation analysis**

Component	Claim or assumption
Therapeutic claim: bioequivalence	Based on evidence presented in Section 2, Dovato® is assumed to be an acceptable pharmacokinetic bridge to co-administration of the individual components
Therapeutic claim: effectiveness	Based on evidence presented in Section 2, effectiveness is assumed to be non-inferior to Genvoya®, Stribild®, Odefsey®, Eviplera® and Triumeq® for the treatment of HIV infection
Therapeutic claim: safety	Based on evidence presented in Section 2, TDF containing regimens (i.e. Stribild®, Eviplera®) are inferior in terms of safety to non-TDF regimens (Dovato®, Triumeq®, Genvoya®, Odefsey®) for the treatment of HIV infection.
Pivotal evidence	Pivotal evidence: GEMINI-1 and GEMINI-2; TANGO: interim 24-week analyses
Supporting evidence	Bioequivalence study: Study 204994
	Prospective studies: PADDLE, ACTG A5353, ASPIRE, LAMIDOL, DOLAM
	Observational studies: Maggiolo 2017, Borghetti 2018, Cicullo 2018, Borghetti 2016, Baldin 2016, Borghetti 2017, Cucchetto 2016, Hidalgo-Tenorio 2017, Yagci-Caglayik 2017, Tan 2018, DOLULAM
Extended assessment of harms evidence	Key studies: (TDF vs non-TDF therapies): Scherzer 2014, Mocroft 2016, Mocroft 2010, Bedimo 2012, Borges 2017
Equi-effective doses	Individual components: DTG/3TC (50/300mg) ≡ DTG 50mg + 3TC 300mg
Direct medicine costs	Part 1: (Individual components): DTG + 3TC Part 2: (alternative FDC therapy): Biktarvy®, Triumeq®, Genvoya®, Odefsey®
Other costs	ABC: HLA-B*5701 testing prior to the commencement (MBS item 71203/73323) Tenofovir: assessment of urinary protein and glucose every 6 months (DHHS 2018; MBS item: 66503)

Source: Table 77, p113 of the submission.
3TC = lamivudine; AEMP = approved ex-manufacturer price; B/E = bioequivalence; DTG = dolutegravir; FDC = fixed dose combination; HIV = human immunodeficiency virus

6.35 The equi-effective dose is described as: Dovato® (DTG/3TC (50/300mg)) ≡ DTG (50mg) + 3TC (300mg).

6.36 The submission stated that given requirements directly related to the use of abacavir (ABC) and tenofovir, a differential in MBS costs between Dovato® and the alternative FDC triple therapies (Biktarvy®, Triumeq®, Genvoya®, Odefsey®) is expected:

- Abacavir (ABC): HLA-B*5701 testing prior to the commencement (MBS Item 71203/73323; $34.50)
- Tenofovir: urinary protein and glucose at baseline and every 6 months (DHHS 2018; MBS Item: 66503; $9.95 at baseline, 6 months and 12 months).

6.37 The cost-minimisation approach versus Biktarvy®, Genvoya®, Stribild®, Odefsey®, Eviplera® and Triumeq® relies on the PBAC accepting that DTG + Truvada® could act as a proxy for other three-drug regimens.

6.38 Table 13 presents results of the cost-minimisation analysis.

Table 13: **Results of the cost minimisation analysis.**

	Drug costs (AEMP)				Additional monitoring costs	Total costs
	Treatment	**30 days**		**1 year**	**1 year**	**1 year**
Part 1: Individual components	Tivicay® DTG (50mg)	$632.27^	$697.78	$8,495.50	NA	$8,495.50
	3TC (300mg)	$65.51				
Part 2: Alternative FDC triple therapy	Triumeq®	$869.13		$10,581.71	MBS Item 71203/73323: $34.50 at commencement	$10,616.21
	Biktarvy®	$900.34		$10,961.64	MBS Item 66503: $9.95 every 6 months (baseline, month 6, month 12) = $29.85	$10,991.49
	Genvoya®	$958.06		$11,644.38		$11,694.28
	Odefsey®	$958.06		$11,644.38		$11,694.28
Lowest cost method for Dovato® = Individual components						
Evaluation estimation of TDF/FDC regimens based on PBS published prices (May 2019)						
Excluded FDC comparators[2]	Stribild®	$868.55*		$10,574.60	MBS Item 66503: $9.95 every 6 months (baseline, month 6, month 12) = $29.85	$10,604.45
	Eviplera®	$868.55*		$10,574.60	MBS Item 66503: $9.95 every 6 months (baseline, month 6, month 12) = $29.85	$10,604.45

Source: Table 79, p114 of the submission, submission's cost-minimisation and financial impact worksheets.

3TC = lamivudine; AEMP = approved ex-manufacturer price; DTG = dolutegravir; HIV = human immunodeficiency virus

^ Accounting for 5% statutory reduction that is applicable for DTG from April 2019. These prices were cross-referenced with current PBS published prices during the evaluation (May 2019)

* These prices were back-calculated using the AEMP to DPMQ calculator in the submission's financial model. The prices without the 34.82% price disclosure reduction corresponded to PBS published prices, and were updated during the evaluation.

6.39 In the cost-minimisation analysis, prices of DTG and all DTG containing FDCs were adjusted to account for a 5% statutory reduction applicable to DTG from April 2019. Review of PBS published prices during the evaluation indicated that the calculated prices were consistent with PBS prices in May 2019.

6.40 In the cost-minimisation analysis, prices for Truvada® and all tenofovir/emtricitabine (TDF/FTC) containing triple-drug FDCs were adjusted to account for a 34.82% reduction due to an anticipated April 2019 price disclosure outcome. Review of current PBS prices during the evaluation (9 May 2019) indicated that the 34.82% reduction to regimens containing TDF/FTC had not been applied. In March 2019, advice from the PBAC was sought on whether the TDF/FTC containing medicines, Atripla®; Eviplera® Stribild®, Truvada® should be removed from the PBS schedule. The advice was sought because prices consistent with the current price of the component drug tenofovir with emtricitabine (Truvada®) could not be agreed as required due to price disclosure price reductions to all PBS-listed brands of tenofovir with emtricitabine. The PBAC advised that there were no reasons why these medicines should remain on the PBS, however recommended that Atripla®, Eviplera® and

[2] As at 1 May 2019, indicative price disclosure-related reductions to Stribild® and Eviplera® of 34.82% have not been applied. If this was to be applied in the future, the indicative AEMP and DPMQ of these FDCs would be $[redacted] and $[redacted], respectively.

Stribild® should remain listed on the PBS for six months, subject to consultation with clinical and community peak bodies. (March 2019 PBAC outcomes, 'Other Matters,'p5).

6.41 From 1 August 2019, the price for Atripla® will reduce to $[redacted] (ex-man) for a pack of 30. The PBAC however maintained its previously expressed view that therapies containing efavirenz, such as Atripla® have inferior safety to non-efavirenz containing therapies for the treatment of HIV infection (dolutegravir/rilpivirine Public Summary Document July 2018, paragraph 7.8).

Drug cost/patient/year: $[redacted]

6.42 The drug cost per patient per course/year is $[redacted] based on a DPMQ of $[redacted], a pack size of 60 tablets and 365.25 days in a year ($[redacted]/60 x 365 = $[redacted]). This compares with $8,853.56 ((DPMQ dolutegravir [$1,311.83] + DPMQ for lamivudine [$143.55])/60 x 365) for DTG + 3TC taken concomitantly. Treatment is ongoing; it is expected that patients would remain on ART treatment for the duration of his or her life.

Estimated PBS usage & financial implications

6.43 This submission was not considered by DUSC.

6.44 The submission followed (i) an epidemiological approach to estimating use in treatment-naïve patients, and (ii) a hybrid epidemiological approach derived from the incidence of HIV-infection and a market share approach for estimating use in treatment switch patients, derived from the prevalent HIV treated population, overlaid with the proportion of virologically suppressed and switching therapy.

6.45 At time of ESC advice, the TGA clinical evaluator did not recommend Dovato® in treatment switch/treatment experienced patients. If Dovato® does not receive TGA approval for these patients, the financial impact estimates would have to be amended.

6.46 The submission had made the same assumptions in calculating certain ART prices after April 2019 price reductions as in the cost-minimisation analysis. During the evaluation these prices were updated to correspond with current PBS published prices (specifically, the current PBS listed prices did not include price disclosure reductions for TDF/FTC containing regimens of Stribild®, Atripla® and Eviplera® as calculated in the submission). Updating the results led to higher estimates of cost savings. The PBAC noted that, as the price for Atripla® would reduce on 1 August 2019; this will need to be adjusted in the financial estimates.

6.47 One consideration that was overlooked in the financial estimates presented is the individual components DTG + 3TC are PBS-listed and the two-drug regimen is already available for use. The submission's estimates of changes in use focus entirely on three-drug FDCs or dolutegravir + two-drug FDCs being substituted. If the submission's clinical claims and descriptions of the rationale for two-drug therapy were to be accepted, then a portion of the replaced therapies would be from the two individual

components of DTG and 3TC. This consideration was not discussed. Given the cost-minimisation price is linked to the individual components, any replacement of DTG + 3TC by Dovato® would not result in any savings for these patients. However, given the recent publication of the results of the GEMINI trials (Cahn 2018), it may not be expected that a large proportion of patients who would be considered for this regimen would already be receiving DTG + 3TC.

6.48 Market share estimates were based on Advisory Board advice (n=9, Attachment 1 to the submission). The financial estimates were sensitive to alternative assumptions. There was substantial uncertainty around what future uptake of Dovato® could be.

6.49 The ESC agreed with the Commentary and considered the estimates were highly uncertain, raising questions as to the acceptability of 2-drug regimens in the Australian context. Noting nearly half the population of people living with HIV in Australia was now aged over 50 (Kirby Institute, 2018)[3], the ESC considered it was likely most were stable on current therapy and was unsure what proportion may consider a switch to a 2-drug regimen.

6.50 Similarly, reasoning for [redacted]% of naïve patients and [redacted]% of switch patients being estimated to be eligible for Dovato® was not adequately discussed. The authors of the publication for the GEMINI trials (Cahn 2018) noted that "*533 (27%) of those screened were not eligible for the study, and the most common reasons for ineligibility were evidence of pre-existing major viral resistance mutations and baseline viral load of less than 1000 copies per mL or more than 500 000 copies per mL*" (p11 of the published article). Given that the TGA indication would be expected to be similar to the trial inclusion criteria, particularly the exclusion of patients with viral resistance mutation, it seems that the [redacted]% eligibility as estimated by the Advisory Board may be an overestimate for treatment-naïve patients.

[3] The Kirby Institute. (2018). HIV in Australia: Annual surveillance short report 2018. Sydney: Kirby Institute, UNSW Sydney.

6.51 Table 14 presents the estimated use and financial implications.

Table 14: **Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Dovato® patients : treatment naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scripts (6.09 per patient)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dovato® patients: treatment switch :	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scripts (6.09 per patient)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of Dovato®						
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for replaced ARTs						
Cost to PBS/RPBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost to PBS/RPBS less copayments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net financial implications						
Net cost to PBS/RPBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost to MBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost to PBS/RPBS/MBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]

Source: Table 92, to 94, pp126-127, Tables 97 and 98, p 129, and Table 102, p131 of the submission.
Prices updated to current PBS published prices during the evaluation.

6.52 After updating prices, estimated savings to Government Health budgets were less than $10 million in Year 1 and $20 - $30 million in Year 6. Over the 6-year estimates, this represents cumulative savings to the government health budget of more than $100 million. This estimate was overwhelmingly driven by savings to the PBS/RPBS from displacing more expensive therapies.

6.53 The ESC noted the potential savings to government are dependent on uptake and will not be fully realised if use is lower than expected. It is unclear whether the estimated savings to the PBS/RPBS are reliable given differences between the overall projected save and the likely save per patient, even against the most costly alternative.

6.54 With the potential delisting of the tenofovir disoproxil-based therapies Atripla®, Eviplera® and Stribild® (paragraph 6.35) the PSCR provided updated financial estimates assuming minimal substitution of these products. However, as the price of Atripla® has now been reduced and is therefore now unlikely to be withdrawn from the PBS, the estimates will need to be revised to account for this. It was noted that the estimates in Table 14 do not account for this subsequent change.

Quality Use of Medicines

6.55 The submission presented additional information regarding pharmacovigilance and risk management activities being conducted in relation to Dovato®. The submission identified a number of important identified risks that will be assessed including hepatotoxicity, hypersensitivity, severe or serious rash, drug resistance, neural tube defects, use in pregnancy and breastfeeding and long-term safety.

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

7 PBAC Outcome

7.1 The PBAC deferred making a recommendation for the Section 100 (Highly Specialised Drugs Program - Community Access) listing of dolutegravir (DTG) with lamivudine (3TC) (Dovato®) fixed dose combination (FDC) for the treatment of HIV infection as it was unclear if the TGA registration will permit use in treatment-experienced patients. For treatment-naïve patients, the PBAC was of a mind to recommend Dovato, however agreed it was appropriate to await further clarity on the likely TGA outcome prior to making a recommendation for the PBS.

7.2 The PBAC considered the evidence presented supported the claims of bioequivalence with concomitantly administered DTG + 3TC. Based on the pooled 48-week and unevaluated 96-week data from the GEMINI trials versus a regimen of DTG and tenofovir disoproxil (TDF) + emtricitabine (FTC) (Truvada®) presented, the PBAC agreed a conclusion of non-inferiority against this regimen in treatment naïve patients was reasonable. The PBAC was also satisfied that a regimen of DTG + Truvada could be a reasonable proxy for other similar three drug regimens (3DRs) in treatment naïve patients.

7.3 The PBAC agreed it was appropriate to await further clarity from the TGA prior to providing advice on its view on the comparative effectiveness and safety of Dovato in treatment experienced patients, and noted there was limited clinical data available in this population (from a 24-week preliminary analysis of the open-label TANGO trial).

7.4 The PBAC considered the data supported a conclusion of non-inferior comparative safety versus a regimen of DTG + Truvada, and by extension other similar 3DR regimens in treatment naïve patients. The PBAC noted the claim of superior safety of non-TDF containing regimens over TDF containing regimens based on renal function and bone toxicity was largely from observational data and recalled it had previously considered there was insufficient evidence for similar claims in regimens containing tenofovir alafenamide (TAF) (paragraph 6.32 refers). The PBAC considered the observational data presented did not provide additional certainty on whether these outcomes were clinically meaningful. The Committee reaffirmed its position from when it considered TAF-containing regimens including Odefsey® and Descovy®, and noted its previous consideration of Biktarvy focused on the NNRTI and boosted INSTI components, not the comparative safety of TDF and TAF.

7.5 The PBAC agreed the clinician's advice in the sponsor hearing was informative and highlighted some treatment-experienced patients might find switching to a 2DR desirable. In particular, the PBAC agreed with the clinician that with the emergence of comorbidities and polypharmacy in an aging prevalent population, some virologically suppressed patients might express a desire to switch to a regimen with fewer agents if suppression is maintained.

7.6 In principle, the PBAC agreed the restrictions should be aligned with similar FDC listings for HIV, however may require additional development if the TGA does not approve use in treatment-experienced patients. The PBAC considered the Draft Product Information (PI) adequately outlines age and weight restrictions requested in the submission and are not necessary in the PBS restriction as HIV prescribers are experienced with appropriate regimen selection for patients. Furthermore, the PBAC agreed the approved PI adequately outlines age and weight restrictions in the current PBS listing of the combination drug abacavir/lamivudine/dolutegravir (Triumeq®) and recommended their removal from the current listing.

7.7 The PBAC accepted concomitant use of DTG + 3TC as an acceptable pharmacokinetic comparator for the fixed-dose combination and other 3DR single tablet regimens used in the treatment of HIV (including Genvoya®, Stribild®, Odefsey®, Eviplera®, Triumeq® and Biktarvy®) as relevant clinical economic comparators. The Committee noted the comparator in the GEMINI trials of DTG + Truvada was not nominated by the submission, however considered it may be a relevant clinical comparator as the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) guidelines class this regimen as a recommended initial option for most people with HIV with level AI evidence[4]. Furthermore, accepting clinical claims for 3DR single tablet regimens relies on accepting DTG + Truvada as a proxy for other regimens.

7.8 The PBAC agreed a price proposal based on the cost of components at the approved ex-manufacturer price was reasonable and Dovato represented a new least costly FDC for HIV infection (based on prices at time of consideration). The PBAC also noted that at the proposed price, Dovato would be less costly than a regimen of DTG + Truvada at time of consideration.

7.9 The PBAC considered the utilisation estimates to be uncertain for a number of reasons, including:

- For treatment naïve patients, the ASHM HIV treatment guidelines classify DTG + 3TC for 'use in certain clinical situations'. The guidelines recommend 3DR regimens of 2 NRTIs plus an INSTI for most people with newly-diagnosed HIV. The PBAC considered that under current treatment guidelines, there may

[4] Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM), 2018. Antiretroviral Guidelines, US DHHS Guidelines with Australian Commentary – What to Start: Initial Combination Regimens for the Antiretroviral-naïve patient. Available at <http://arv.ashm.org.au/what-to-start-initial-combination-regimens-for-the-antiretroviral-naive-patient/> accessed 10 July 2019.

be limited acceptability of Dovato in treatment-naïve patients;

- The PBAC considered the epidemiological approach likely overestimated the incident HIV population over time due to factors such as the recent listing of pre-exposure prophylaxis (PrEP) and considered a market share approach would have been appropriate; and
- A regimen of concomitant DTG + 3TC can already be prescribed on the PBS and its use is uncommon in practice.

Noting the uncertainties as to whether the TGA will approve Dovato for use in treatment-experienced patients, the PBAC provided advice regarding the use of 2DRs in this population more generally rather than for Dovato specifically:

- The use of 3DRs in practice is well established and it is unclear how many patients will seek to switch to a regimen with fewer drugs. The PBAC agreed with the ESC and was uncertain how acceptable this regimen will be to treatment-experienced patients;
- The PBAC considered the eligible treatment-experienced population and likely uptake in this group was likely overestimated. Noting the submission used an expert panel to assist with estimating the eligible population, the PBAC remained uncertain how desirable 2DRs are in practice. Factors such as comorbidities, polypharmacy and risk of drug-drug interactions in an aging prevalent population may increase the appeal of 2DRs for some patients, whilst others who remain stable on current treatment long-term may have no desire to switch. The PBAC considered there is a place for 2DRs in treatment-experienced patients and while some patients may realise a safety benefit, it was likely a relatively small number of patients would seek to change regimen; and
- The PBAC noted the fixed dose combination of dolutegravir + rilpivirine (Juluca®) was already listed on the PBS only for treatment-experienced patients and considered it may have already absorbed a portion of the treatment-experienced market willing to switch to a 2DR.

7.10 Despite uncertainty with the likely eligible population and uptake, the PBAC noted that at the proposed price, even modest uptake would result in savings to the PBS, as it would replace therapies that are more expensive.

7.11 The PBAC agreed it would finalise its advice on whether or not to recommend Dovato at its next available opportunity following provision of the ACM advice and Delegate's decision (if required) and clarity on whether the TGA will approve use in treatment-experienced patients.

7.12 The PBAC noted it has previously advised that single tablet FDCs for HIV infection should not be treated as interchangeable with any other drugs and agreed in principle this should apply to Dovato if recommended.

7.13 The PBAC advised in principle that Dovato is not suitable for prescribing by nurse practitioners as prescribing items in the Section 100 is limited to medical practitioners.

7.14 The PBAC advised in principle the Early Supply Rule should apply, similar to other PBS listings for HIV therapies.

7.15 The PBAC noted the recommended restriction changes to remove age and weight population criteria from the Triumeq listings (item 10345L). The PBAC advised this change could occur independently of a recommendation for Dovato.

Outcome:
Deferred

8 Changes to other listings

8.1 Remove age and weight restrictions from 10345L – abacavir/lamivudine/dolutegravir (Triumeq®).

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.