6.06 TRUVADA®, tablets, emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg, Gilead Sciences Pty Ltd.

To improve the readability of this document, Truvada is generally identified by its brand name. Where the form of the drug within Truvada is described, the Australian Medicines Terminology medicinal product unit of use (MPUU) is used.

1 Purpose of Application

1.1 Section 100 Highly Specialised Drugs Program Authority Required listing for emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg tablet (Truvada) as an oral pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at substantial risk.

2 Requested listing

2.1 The proposed listing is presented below.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
TENOFOVIR DISOPROXIL FUMARATE 300 MG + EMTRICITABINE 200 MG ORAL TABLET, 30	1	2	$[redacted]	TRUVADA	GILEAD SCIENCES PTY LTD

Section 100 Highly Specialised Drugs Program (Community Access) Authority Required

Category / Program	Section 100 – Highly Specialised Drugs Program (Community Access)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	
Severity:	
Condition:	Chemoprophylaxis of HIV-1 infection
PBS Indication:	To reduce the risk of sexually acquired HIV infection in adults at substantial risk of HIV infection.
Treatment phase:	
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☒Authority Required - Telephone ☒*Authority Required - Emergency* ☒Authority Required - Electronic ☐Streamlined
Treatment criteria:	Patient must be involved in an approved pre-exposure prophylaxis service *AND* Must be treated by an anti-retroviral therapy approved prescriber
Clinical criteria:	Patient must be considered at substantial risk of sexually acquired HIV-infection,

	where substantial risk is defined as an annual incidence of HIV infection in the absence of pre-exposure prophylaxis of 3% *AND* Patient must return a negative HIV-1 test prior to initiating treatment *AND* Patient must return a negative HIV-1 test within 7 days of initiating treatment *AND* Patient must continue to return negative HIV-1 tests at 3 monthly intervals throughout treatment
Population criteria:	Patient must be 18 years or older

2.2 The PBAC noted that the proposed price for Truvada when used in the PrEP setting is [redacted] for its use as treatment for patients with HIV.

2.3 The PBAC noted that the submission proposed that, in order to receive Truvada as PrEP, subjects must be enrolled in an approved PrEP service and treated by an ART approved prescriber. The submission did not clarify how the "approved PrEP services" will be financed and organised.

2.4 In order to receive Truvada as PrEP, the submission proposed that subjects must be considered at substantial risk of sexually acquired HIV-infection. Substantial risk was defined in the submission as an annual incidence of HIV infection (in the absence of PrEP) of 3%. The submission proposed the use of Australian data to develop a simple risk calculator for use in a clinical setting to establish whether an individual is at 3% or greater annual risk of acquiring HIV and therefore eligible for the proposed PBS listing. Such a risk calculator does not yet exist for the Australian population and the criteria for defining risk will primarily be based on self-reported behaviour. The ESC considered restricting use to the population with substantial risk was not well justified, especially given the patient population is difficult to define.

2.5 The Pre-Sub-Committee Response (PSCR, p1) noted that risk-based eligibility assessment was currently in place in the PrEP demonstration projects operating across Australia. The PSCR suggested that the frameworks currently in use could be adapted to produce a risk calculator similar to the sample identified in the submission. The ESC agreed that the methods being used to determine eligibility for the demonstration projects might provide an appropriate starting point for the development of a risk calculator.

2.6 The PBAC noted that the submission had tried to limit the population that would be eligible for treatment to those at highest risk in order to improve the cost effectiveness. However, the PBAC considered that the cost-effectiveness estimates were unreliable and that attempts to limit the eligible population in the ways proposed by the submission would not be practical or appropriate. The PBAC noted that each individual's risk would need to be determined based on their self-reported potential future behaviour, and that the proposed 3% annual incidence was arbitrary. It is

unlikely that a risk calculator would be able to accurately estimate future risk, and the proposed cut-off was not justified.

2.7 The submission provided a cost-utility analysis comparing "Truvada + standard of care" with "standard of care".

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

3 Background

3.1 Truvada was TGA registered for PrEP on 6 May 2016.
The registered indication is: Pre-Exposure Prophylaxis: in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk.

Truvada was TGA registered on 22 September 2005 for the treatment of HIV infected adults, in combination with other antiretroviral agents.

3.2 Truvada is currently available on the PBS for the treatment of HIV.

4 Clinical place for the proposed therapy

4.1 The submission proposed PBS listing for Truvada to reduce the risk of sexually acquired HIV infection in adults at substantial risk of HIV infection. Substantial risk was defined as an annual incidence of HIV infection in the absence of pre-exposure prophylaxis of 3%.

4.2 The proposed place of Truvada is in the reduction of risk of HIV infection.

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

5 Comparator

5.1 The submission nominated "standard of care" (SOC) as the main comparator. SOC for HIV prevention in Australia comprises public health initiatives aimed at encouraging safer sex practices and regular HIV testing in high risk groups (primarily, but not limited to men who have sex with men (MSM)).

5.2 The PBAC agreed this was the appropriate comparator, noting however that as Truvada is intended to be used in combination with, and not as a substitute for other methods to reduce the risk of HIV transmission, the appropriate comparison is therefore: "Truvada + SOC" versus "SOC".,

5.3 The PBAC noted that safe sex practices (as a consequence of the SOC measures) may be different in subjects using Truvada compared to subjects who do not use Truvada. The implications of that change in safe sex practices associated with

Truvada use for HIV transmission and the incidence of other sexually acquired infections is unknown.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (92), health care professionals (2) and organisations (19) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of use of Truvada for PrEP, including reduction of risk of transmission of HIV, increased screening for HIV and other STIs, and reduced anxiety of contraction of HIV for people at risk. The comments also provided some insight to the way Truvada might be used for PrEP in clinical practice, including of reasons individuals might seek to initiate Truvada for PrEP and likely patterns of use (eg duration, continuous vs intermittent use, likely triggers for stopping etc).

Clinical trials

6.3 The submission included 6 head-to-head randomised trials comparing Truvada + SOC to SOC. In the submission, the 6 included randomised trials (iPrEx, Partners PrEP, TDF2, PROUD, FEM-PrEP and VOICE) were meta-analysed.

6.4 Details of the trial publications 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		
iPrEx NCT: 00458393	Chemoprophylaxis for HIV Prevention in Men. Grant RM, Lama JR, Anderson PL, McMahon BS, et al. Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men. Amico K, McMahan V, Goicochea P, Vargas L, et al. Supporting study product use and accuracy in self-report in the iPrEx study: next step counseling and neutral assessment. Amico KR, Marcus JL, McMahan V, Liu A, et al. Study product adherence measurement in the iPrEx placebo-controlled trial: concordance with drug detection. Anderson PL, Glidden DV, Liu A, Buchbinder S, et	24 March 2011 *New Engl J Med* 2010; 363:2587-2599. *AIDS & Behavior* 2012; 16 (5):1243-1259. *Journal of Acquired Immune Deficiency Syndromes* 2014; 66 (5):530-537. *Science Translational Medicine* 2012; 4 (151):151ra125.

Trial ID	Protocol title/ Publication title	Publication citation
	al. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men.	
	Buchbinder SP, Glidden DV, Liu AY, McMahan V, et al. HIV pre-exposure prophylaxis in men who have sex with men and transgender women: A secondary analysis of a phase 3 randomised controlled efficacy trial.	*The Lancet Infectious Diseases* 2014; 14 (6):468-475.
	Gilmore HJ, Liu A, Koester KA, Amico KR, et al. Participant experiences and facilitators and barriers to pill use among men who have sex with men in the iPrEx pre-exposure prophylaxis trial in San Francisco.	*AIDS Patient Care & STDs* 2013; 27 (10):560-566.
	Guanira JV, Leigler T, Kallas E, Schechter M, et al. Streamlining HIV Testing for HIV Preexposure Prophylaxis.	*Journal of Clinical Microbiology* 2015; 53 (1):179-183.
	Kuebler PJ, Mehrotra ML, McConnell JJ, Holditch SJ, et al. Cellular immune correlates analysis of an HIV-1 preexposure prophylaxis.	*Proceedings of the National Academy of Sciences of the Unites States of America* 2015; 112 (27):8379-8384.
	Liegler T, Abdel-Mohsen M, Bentley LG, Atchison R, et al. HIV-1 drug resistance in the iPrEx preexposure prophylaxis trial.	*Journal of Infectious Diseases* 2014; 210 (8):1217-1227.
	Liu A, Glidden DV, Anderson PL, Amico KR, et al. Patterns and correlates of PrEP drug detection among MSM and transgender women in the Global iPrEx Study.	*Journal of Acquired Immune Deficiency Syndromes* 2014; 67 (5):528-537.
	Marcus JL, Glidden DV, Mayer KH, Liu AY, et al. No evidence of sexual risk compensation in the iPrEx trial of daily oral HIV preexposure prophylaxis.	*PLoS ONE* 2013; 8 (12):e81997.
	Marcus JL, Glidden DV, McMahan V, Lama JR, et al. Daily oral emtricitabine/tenofovir preexposure prophylaxis and herpes simplex virus type 2 among men who have sex with men.	*PLos ONE* 2014; 9 (3):e91513.
	Mulligan K, Glidden DV, Anderson PL, Liu A, et al. Effects of emtricitabine/tenofovir on bone mineral density in HIV-negative persons in a randomised, double-blind, placebo-controlled trial.	*Clinical Infectious Diseases* 2015; 61 (4):752-580.
	Mulligan K, Glidden DV, Anderson PL, McMahan V, Guanira JV, Lama JR. Decreases in cholesterol in HIV-seronegative men using emtricitabine/tenofovir pre-exposure prophylaxis: Lipid results of iPrEx.	*15th International Workshop on Co-morbidities and Adverse Drug Reactions in HIV* 2013. *AIDS* 2014; 28 (6):851-859.
	Solomon MM, Lama JR, Glidden DV, Mulligan K, et al. Changes in renal function associated with oral emtricitabine/tenofovir disoproxil fumarate use for	

Trial ID	Protocol title/ Publication title	Publication citation
	HIV pre-exposure prophylaxis. Tangmunkongvorakul A, Chariyalertsak S, Amico KR, Saokhieo P, et al. Facilitators and barriers to medication adherence in an HIV prevention study among men who have sex with men in the iPrEx study in Chiang Mai, Thailand.	*AIDS Care* 2013; 25 (8):961-967.
Partners PrEP NCT: 00557245	Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples.	14 November 2011
	Baeten, JM, Donnell, D, Ndase, P, Mugo, NR, Campbell, JD, Wangisi, J, et al. Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women.	*New Engl J Med* 2012; 367 (5):399-410.
	Baeten JM, Donnell D, Mugo NR, Ndase P, et al. Single-agent tenofovir versus combination emtricitabine plus tenofovir for pre-exposure prophylaxis for HIV-1 acquisition: an update of data from a randomised, double-blind, phase 3 trial.	*The Lancet Infectious Diseases* 2014; 14 (11):1055-1064.
	Celum C, Morrow R, Donnell D, Hong T, et al. Daily Oral Emtricitabine/Tenofovir Pre-Exposure Prophylaxis and Prevention of HSV-2 Acquisition Among Heterosexual Men and Women.	*Sexually Transmitted Infections* 2013; 89:A265.
	Donnell D, Baeten JM, Bumpus NN, Brantley J, et al. HIV protective efficacy and correlates of tenofovir blood concentrations in a clinical trial of PrEP for HIV prevention.	*Journal of Acquired Immune Deficiency Syndromes* 2014; 66 (3):340-348.
	Haberer JE, Baeten JM, Campbell J, Wangisi J, et al. Adherence to antiretroviral prophylaxis for HIV prevention: a substudy cohort within a clinical trial of serodiscordant couples in East Africa.	*PLoS Medicine* 2013; 10 (9):e1001511.
	Haberer J, Baeten J, Celum C, Katibira E, et al. High adherence among HIV-1 serodiscordant couples in the partners PrEP ancillary adherence study.	*7th International Conference on HIV Treatment and Prevention Adherence* 2012.
	Heffron R, Mugo N, Were E, Kiarie J, et al. Preexposure prophylaxis is efficacious for HIV-1 prevention among women using depot medroxyprogesterone acetate for contraception.	*AIDS* 2014; 28 (18):2771-2776.
	Kintu A, Hankinson SE, Balasubramanian R, Ertel K, et al. Sexual Relationships Outside Primary Partnerships and Abstinence Are Associated With Lower Adherence and Adherence Gaps: Data From the Partners PrEP Ancillary Adherence Study.	*Journal of Acquired Immune Deficiency Syndromes* 2015; 69 (1):36-43.
	Lehman D, Baeten J, McCoy c, Weis J, et al. PrEP	*21st Conference on Retroviruses and Opportunistic*

Trial ID	Protocol title/ Publication title	Publication citation
	Exposure and the Risk of Low-frequency Drug Resistance.	*Infections* 2014.
	Matthews LT, Heffron R, Mugo NR, Cohen CR, et al. High medication adherence during periconception periods among HIV-1-uninfected women participating in a clinical trial of antiretroviral pre-exposure prophylaxis.	*Journal of Acquired Immune Deficiency Syndromes* 2014; 67 (1):91-97.
	Mugo NR, Hong T, Celum C, Donnell D, et al. Pregnancy incidence and outcomes among women receiving preexposure prophylaxis for HIV prevention: a randomised clinical trial.	*JAMA* 2014; 312 (4):362-371.
	Mugwanya KK, Donnell D, Celum C, Thomas KK, et al. Sexual behaviour of heterosexual men and women receiving antiretroviral pre-exposure prophylaxis for HIV prevention: a longitudinal analysis.	*The Lancet Infectious Diseases* 2013; 13 (12):1021-1028.
	Mugwanya KK, Wyatt C, Celum C, Donnell D, et al. Changes in glomerular kidney function among HIV-1-uninfected men and women receiving emtricitabine-tenofovir disoproxil fumarate preexposure prophylaxis: a randomized clinical trial.	*JAMA Internal Medicine* 2015; 175 (2):246-254.
	Mujugira A, Baeten JM, Donnell D, Ndase P, Mugo NR, Barnes L, et al. Characteristics of HIV-1 serodiscordant couples enrolled in a clinical trial of antiretroviral pre-exposure prophylaxis for HIV-1 prevention: the Partners PrEP Study.	*PLoS One* 2011; 6 (10):e25828.
	Murnane PM, Celum C, Mugo N, Campbell JD, et al. Efficacy of preexposure prophylaxis for HIV-1 prevention among high-risk heterosexuals: subgroup analyses from the Partners PrEP Study.	*AIDS* 2013; 27 (13).
	Murnane PM, Heffron R, Ronald A, Bukusi EA, et al. Pre-exposure prophylaxis for HIV-1 prevention does not diminish the pregnancy prevention effectiveness of hormonal contraception.	*AIDS* 2014; 28 (12):1825-1830.
	Ndase P, Celum C, Campbell J, Bukusi E, et al. Successful discontinuation of the placebo arm and provision of an effective HIV prevention product after a positive interim efficacy result: the partners PrEP study experience.	*Journal of Acquired Immune Deficiency Syndromes* 2014; 66 (2):206-212.
	Ndase P, Celum C, Kidoguchi L, Ronald A, et al. Frequency of false positive rapid HIV serologic tests in African men and women receiving PrEP for HIV prevention: implications for programmatic roll-out of biomedical interventions.	*PLoS ONE* 2015; 10 (4):e0123005.
	Pattacini L, Murnane PM, Baeten JM, Fluharty TR,	*Journal of Infectious Diseases* 2015; 211

Trial ID	Protocol title/ Publication title	Publication citation
	et al. Antiretroviral Pre-Exposure Prophylaxis Does Not Enhance Immune Responses to HIV in Exposed but Uninfected Persons.	(12):1943-1952.
	Psaros C, Haberer JE, Katabira E, Ronald A, et al. An intervention to support HIV preexposure prophylaxis adherence in HIV-serodiscordant couples in Uganda.	*Journal of Acquired Immune Deficiency Syndromes* 2014; 66 (5):522-529.
	Were EO, Heffron R, Mugo NR, Celum C, et al. Pre-exposure prophylaxis does not affect the fertility of HIV-1-uninfected men.	*AIDS* 2014; 28 (13):1977-1982.
TDF2 NCT:00448669	Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, et al. Antiretroviral Preexposure Prophylaxis for Heterosexual HIV Transmission in Botswana.	*New Engl J Med* 2015; 367:423-434.[1]
	Chirwa LI, Johnson JA, Niska RW, Segolodi TM, et al. CD4+ cell count, viral load, and drug resistance patterns among heterosexual breakthrough HIV infections in a study of oral preexposure prophylaxis.	*AIDS* 2014; 28 (2):223-226.
	Kasonde M, Niska RW, Rose C, Henderson FL, et al. Bone Mineral Density Changes among HIV-Uninfected Young Adults in a Randomised Trial of Pre-Exposure Prophylaxis with Tenofovir-Emtricitabine or Placebo in Botswana.	*PLoS ONE* 2014; 9 (3):e90111.
PROUD NCT:02065986	McCormack S, Dunn DT, Desai M, Dolling DI, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial.	*The Lancet* 2016; 387 (10013):53-60.
	Roche M, Youssef E, Gilleece Y, McCormack S, et al. Do patients adherent on PREP exposed to HIV have seroconversion symptoms and falsely reactive HIV tests?	2014
FEM-PrEP NCT:00625404	Van Damme L, Corneli A, Ahmed K, Agot K, et al. Preexposure Prophylaxis for HIV infection among African Women.	*New Engl J Med* 2012; 367:411-422.
	Corneli AL, Deese J, Wang M, Taylor D, et al. FEM-PrEP: adherence patterns and factors associated with adherence to a daily oral study product for pre-exposure prophylaxis.	*Journal of Acquired Immune Deficiency Syndromes* 2014; 66 (3):324-331.
	Corneli A, Wang M, Agot K, Ahmed K, et al. Perception of HIV risk and adherence to a daily, investigational pill for HIV prevention in FEM-PrEP.	*Journal of Acquired Immune Deficiency Syndromes* 2014; 67:555-563.
	Grant RM, Liegler T, Defechereux P, Kashuba AD, et al. Drug resistance and plasma viral RNA level after ineffective use of oral pre-exposure prophylaxis in women.	*AIDS* 2015; 29 (3):331-337.

Trial ID	Protocol title/ Publication title	Publication citation
	Headley J, Lemons A, Corneli A, Agot K, et al. The sexual risk context among the FEM-PrEP study population in Bondo, Kenya and Pretoria, South Africa.	*PLoS ONE* 2014; 9 (9):e106410.
	Mandala J, Nanda K, Wang M, De Baetselier I, et al. Liver and renal safety of tenofovir disoproxil fumarate in combination with emtricitabine among African women in a pre-exposure prophylaxis trial.	*BMC Pharmacology and Toxicology* 2014; 15:77.
	Owino F, Mandala J, Ambia J, Agot K, Van Damme L. Neurological syndrome in an HIV-prevention trial participant randomized to daily tenofovir disoproxil fumarate (300 mg) and emtricitabine (200 mg) in Bondo, Kenya.	*International Medical Case Reports Journal* 2013; 6:91-93.
	Todd CS, Deese J, Wang M, Hubacher D, et al. Sino-implant (II)® continuation and effect of concomitant tenofovir disoproxil fumarate-emtricitabine use on plasma levonorgestrel concentrations among women in Bondo, Kenya.	*Contraception* 2015; 91 (3):248-252.
VOICE NCT:00705679	Marrazzo JM, Ramjee G, Richardson BA, Gomez K, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women.	*New Engl J Med* 2015; 372 (6):509-518.
	Balkus JE, Nair G, Montgomery ET, Mishra A, et al. Age-disparate partnerships and risk of HIV-1 acquisition among South African women participating in the VOICE trial.	*Journal of Acquired Immune Deficiency Syndromes* 2015; 70 (2):212-217.
	Nair G, Balkus JE, Marrazzo JM, Ramjee G, et al. Baseline Predictors of HIV-1 Acquisition Among Women Participating in MTN-003 (VOICE).	*21th Conference on Retroviruses and Opportunistic Infections* 2014.
	Parikh UM, Eskay KA, Hardesty RL, Kelly C, et al. HIV-1 Resistance Outcomes in Seroconverters from MTN 003 (VOICE).	*21th Conference on Retroviruses and Opportunistic Infections* 2014.
	Marrazzo J, Rabe L, Kelly C, Livant T, et al. Herpes simplex virus (HSV) infection in the VOICE (MTN 003) study: Pre-exposure prophylaxis (PrEP) for HIV with daily use of oral tenofovir, oral tenofovir-emtricitabine, or vaginal tenofovir gel.	*Sexually Transmitted Infections* 2013.

Source: Appendix 1, Table B-5 and Table B-6, pp 41-42 of the submission.
[1]The submission reported this article to be published in 2015 (see Table B-4), but the article was published in 2012.

6.5 The key features of the direct randomised trials are summarised in the table below.

Table 2: Key features of the included evidence

Trial	N	Design, follow-up	Risk of bias	Population	Outcomes	Use in modelled evaluation
Truvada + SOC vs. SOC						
iPREX	2,441	R, DB	Low	MSM at high risk	Incidence of	Efficacy in

		3,324 person-years		(Peru, Ecuador, Brazil, USA, Thailand, South Africa)	HIV seroconversion	highly adherent subjects
Partners PrEP	3,154	R, DB 7,830 person-years	Low	Partners of seropositive patients (Kenya, Uganda)	Incidence of HIV seroconversion	Efficacy in highly adherent subjects
TDF2	1,216	R, DB 1,563 person-years	Low	Heterosexuals (Botswana)	Incidence of HIV seroconversion	Not used
PROUD	523	R, OL 465 person-years	High	MSM at high risk (England)	Incidence of HIV seroconversion[1]	Not used
FEM-PrEP	2,056	R, DB 1,407 person-years	Low	Women (Kenya, South Africa, Tanzania)	Incidence of HIV seroconversion	Not used
VOICE	2,002	R, DB 5,509 person-years	Low	Women (South Africa, Uganda, Zimbabwe)	Incidence of HIV seroconversion	Not used
Meta-analysis	11,392	Included all of the above; assessed incidence of HIV seroconversion				Not used

Source: compiled during the evaluation.
Abbreviations: DB = double blind, MSM = men who have sex with men, OL = open label, R = randomised, SOC = standard of care.
[1]Originally planned outcomes were time to accrual of 500 participants and retention at 12 and 24 months from randomisation.

6.6 The ESC had a number of concerns about the applicability of the trial data to the Australian setting, including that a large proportion of the data was generated in communities known to have a substantially higher incidence of HIV infection (and therefore higher risk) than the Australian population. The ESC noted that the trials assessed the efficacy of Truvada together with encouragement of safe sex practices, and it is unknown if safe sex practices would be utilised to the same extent in the Australian population. The impact of these differences on the effectiveness of Truvada in clinical practice is unclear. The ESC also noted the existence of community information campaigns promoting Truvada PrEP in the absence of condoms as safe sex. The PBAC agreed that the available data may not be representative of the proposed PBS population, and that this raises uncertainties about whether the results observed in the studies would be realised in the clinical setting.

Comparative effectiveness

6.7 The results of the clinical trials and meta-analysis are presented in the table below. The meta-analysis provided in the submission is considered to be of limited value due to the highly heterogeneous combination of trials. The efficacy results of the clinical trials ranged from a RRR of -0.04 to a RRR of 0.86. The meta-analysed efficacy estimate was 0.50 (95% CI: 0.16, 0.70). Given the heterogeneity between the trials, this pooled estimate is not very informative. The meta-analysed efficacy estimate was not used in the economic evaluation.

6.8 The ESC noted that there was little information provided about the subjects in the studies in whom Truvada failed to prevent transmission of HIV.

Table 3: Results of HIV seroconversion events at the primary efficacy endpoint across the direct randomised trials,

modified intention to treat

Trial ID	Truvada + SOC n with event/N	SOC n with event/N	Risk estimate (95% CI)	RRR (95% CI)	p-value
iPrEx	36/1,224	64/1,217	HR = 0.56 (0.37, 0.85)	0.44 (0.15, 0.63)	0.005
Partners PrEP	13/1,576	52/1,578	HR = 0.25 (0.13, 0.45)	0.75 (0.55, 0.87)	<0.0001
TDF2	9/610	24/606	NR	0.62 (0.22, 0.83)	0.03
PROUD	3/268	20/255	NR	0.86 (0.64, 0.96)	NR
FEM-PrEP	33/1,024	35/1,032	HR = 0.94 (0.59, 1.52)	0.06 (-0.52, 0.41)	0.81
VOICE	61/994	60/1,008	HR = 1.04 (0.73, 1.49)	-0.04 (-0.49, 0.27)	0.81
Pooled result	255/5,696	155/5,696	Mantel-Haenzael random effects RR = 0.50 (0.30, 0.84)	0.50 (0.16, 0.70)	NR
Chi-square for heterogeneity: 28.13, P<0.0001. I^2 statistic with 95% uncertainty interval =82%.					

Source: Tables B-24, B-29, B-32, B-33, B-34, B-36, B-37 and B-38, /pp 73, 79, 82, 85, 86, 89, 90 and 94 of the submission.
Abbreviations: HR = hazard ratio, NR = not reported, RRR = relative risk difference.

6.9 The following table presents results for the subjects with high adherence (based on quantifiable drug concentrations) in the iPrEx, Partners PrEP, FEM-PrEP and VOICE trials. Different approaches to these case-control analyses were used in the various studies. Additional information is provided below the table as well as in section B.6 of the submission.

Table 4: Results of HIV seroconversion events dependent on high adherence, modified intention to treat

Trial ID		n / N subjects with quantifiable drug concentrations	Risk estimate (95% CI)	RRR (95% CI)	p-value
iPrEx,	Case (HIV+)	3/34 (9%)	OR = 12.87 (1.67, 99.34)	0.92 (0.40, 0.99)	<0.001
	Control (HIV-)	22/43 (51%)			
Partners PrEP	Case (HIV+)	3/12 (25%)	HR = 0.10 (0.02, 0.44)	0.90 (0.56, 0.98)	0.002
	Control (HIV-)	375/465 (80.6%)			
FEM-PrEP[1]	Case (HIV+)	7/27 (26%)	NR	NR	0.70[6]
	Control (HIV-)	27/78 (35%)			
FEM-PrEP[2]	Case (HIV+)	7/33 (21%)	NR	NR	0.13[6]
	Control (HIV-)	35/95 (37%)			
FEM-PrEP[3]	Case (HIV+)	4/27 (15%)	NR	NR	0.68[6]
	Control (HIV-)	19/78 (24%)			
VOICE[4]	Case (HIV+)	17/57 (30%)	HR = 1.25 (0.61, 2.58)	-0.25 (-1.58, 0.39)	0.54
	Control (HIV-)	45/142 (32%)			
VOICE[5]	Case (HIV+)	24/61 (39%)	HR = 0.83 (0.39, 1.76)	0.17 (-0.76, 0.61)	0.62
	Control (HIV-)	77/148 (52%)			

Source: Tables B-27, B-31 and B-37, pp 76, 81, 88 and 90 of the submission.
Abbreviations: NR = not reported, RRR = relative risk reduction.
[1]At the start of the infection window.
[2]At the end of the infection window.
[3]At both the start and the end of the infection window.
[4]These results are for detectable tenofovir at the 1st quarterly visit.
[5]These results are for ever having tenofovir detection in plasma samples.

[6]After adjustment for age, unprotected sex, and use of injectable contraception.

6.10 In the iPrEx trial, the RRR of infection with Truvada in subjects with >50% self-reported pill use was 50% (95% CI: 18%, 70%). The RRR of infection in subjects with >90% self-reported pill use was 73% (95% CI: 41%, 88%). Instead of adherence based on self-reported pill use, the submission based its efficacy for adherent subjects on the results of case-control analyses based on quantifiable drug concentrations.

6.11 The ESC noted that the efficacy of Truvada was highly dependent on adherence. Likely adherence in the PBS population is unknown, but 'real life' adherence is generally accepted to be lower than what is observed in clinical trials. It is not clear if subjects at high risk of contracting HIV due to self-reported low adherence to other 'safe sex' practices would also have lower adherence to medication.

6.12 The efficacy of Truvada in the economic evaluation was based on the outcomes from highly adherent subjects from the iPrEx trial and the Partners PrEP trial, based on case-control analyses. The results of these non-randomised analyses are potentially biased. The ESC noted that for the iPrEX and Partners PrEP case control analyses, baseline characteristics were not presented for the cases and controls and hence the potential for bias could not be assessed. It is possible that individuals who were highly adherent to PrEP were also more adherent to safe sex recommendations putting them at lower baseline risk of infection than the broader study population; this would overestimate the benefit of adherence to PrEP. Furthermore, similar analyses were performed with data from the FEM-PrEP trial and the VOICE trial, but these trials did not show efficacy of Truvada in the adherent subgroups. According to the submission this was due to the overall adherence being extremely low in these trials.

6.13 The clinical trials had a median duration of ~2 years. Subjects in clinical practice are likely to use Truvada for longer periods of time (potentially indefinitely) and may stop and start treatment as their risk changes. There is insufficient information to evaluate the potential effect of prolonged and intermittent use on the effectiveness of Truvada. The economic evaluation assumed efficacy and adherence remained constant over time.

6.14 The clinical trials were performed in a number of countries (excluding Australia). Average baseline HIV risk may differ between the clinical trials and the eligible Australian population. None of the countries in the studies had HIV prevalence as low as Australia. The seroconversion rates in the placebo arms of the trials ranged from 2% in the Partners PrEP trial to ~9% in the deferred arm of PROUD. HIV prevalence among Australian MSM is approximately 10%[1]. Prevalence in proposed 'high risk' population is unknown, as this population is not clearly defined.

Comparative harms

6.15 The use of Truvada appeared to be well tolerated across all included clinical trials, with comparable incidence of serious adverse events between Truvada and placebo groups. Gastrointestinal adverse events (in particular nausea and vomiting) were

[1] The Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia Annual Surveillance Report 2014 HIV Supplement. The Kirby Institute, UNSW, NSW 2052

more common in subjects receiving Truvada compared with placebo, but most events occurred in the first month and resolved with continued exposure. Long-term safety of Truvada as PrEP was unknown. Potential concerns included the long-term impact on bone loss and renal function. Furthermore, safety concerns may exist for subgroups that were not assessed separately (e.g. subjects with high adherence) and subgroups that were largely excluded from clinical trials (e.g. subjects with hepatitis B infection).

6.16 The use of Truvada may lead to a de-prioritisation of other risk-mitigating practices (e.g. increased unprotected anal sex with potentially infected partners). This was not considered in the model base case. The Product Information states that 'Truvada should only be used for PrEP as part of a comprehensive prevention strategy including other HIV-1 prevention measures, because TRUVADA is not always effective in preventing the acquisition of HIV-1'. The TGA Delegate's Overview expressed concern about Truvada being perceived as alternative to the use of condoms and since Truvada is not 100% effective, decreased condom use may increase the risk of acquiring HIV as well as other sexually transmitted infections. In the VicPrEP project, the proportion use of condom in casual sex acts reduced.

6.17 Low adherence to Truvada could lead to an increased level of resistance to this drug which forms the backbone of many ART regimens. The potential impact of drug resistance was not included in the economic evaluation. This may overestimate the benefits of Truvada. Careful monitoring will be necessary to confirm if the frequency of emerging new resistances in reality will be as low as that documented in the clinical trials. ESC noted that any resistance to Truvada could have implications not only for HIV treatment, but also for the treatment of Hepatitis B infection.

7 Benefits/harms

7.1 A summary of the comparative benefits and harms for Truvada in combination with SOC (eg safer sex practices and regular HIV testing) versus SOC is presented in the table below.

Table 5: Summary of comparative benefits and harms for Truvada + SOC and SOC

Trial	Truvada + SOC	SOC	RRR (95% CI)	Event rate/100 subjects[1]		RD (95% CI)
				Truvada + SOC	SOC	
Benefits						
HIV seroconversion						
iPrEx	36/1,224	64/1,217	0.44 (0.15, 0.63)	2.9	5.3	0.023 (0.007, 0.039)
Partners PrEP	13/1,576	52/1,578	0.75 (0.55, 0.87)	0.8	3.3	0.025 (0.015, 0.035)
TDF2	9/610	24/606	0.62 (0.22, 0.83)	1.5	4.0	0.025 (0.007, 0.045)
PROUD	3/268	20/255	0.86 (0.64, 0.96)	1.1	7.8	0.067 (0.033, 0.108)
FEM-PrEP	33/1,024	35/1,032	0.06 (-0.52, 0.41)	3.2	3.4	0.002 (-0.014, 0.018)
VOICE	61/994	60/1,008	-0.04 (-0.49, 0.27)	6.1	6.0	-0.002 (-0.023, 0.019)
Meta-analysis (all of the above)	255/5,696	155/5,696	0.50 (0.16,	4.5	2.7	-0.018 (-0.024, -

Trial	Truvada + SOC	SOC	RRR (95% CI)	Event rate/100 subjects[1]		RD (95% CI)
				Truvada + SOC	SOC	
			0.70)			0.011)
Harms						
	Truvada + SOC	**SOC**	**RRR (95% CI)**	**Event rate/100 subjects[1]**		**RD (95% CI)**
				Truvada + SOC	**SOC**	
Nausea						
iPrEx	20/1,251	9/1,248	-1.22 (-3.85, -0.01)	1.6	0.7	-0.009 (-0.018, 0.000)
Partners PrEP	538/33,125[2]	487/33,087[2]	-0.10 (-0.25, 0.02)	1.6	1.5	-0.002 (-0.003, 0.000)
TDF2	113/611	43/608	-1.62 (-2.65, -0.87)	18.5	7.1	-0.114 (-0.151, -0.077)
FEM-PrEP	50/1,025	32/1,033	-0.57 (-1.43, -0.02)	4.9	3.1	-0.018 (-0.035, -0.001)
VOICE	8/1,003[3]	15/1,009[3]	0.46 (-0.26, 0.77)	0.8	1.5	0.007 (-0.003, 0.017)
Vomiting						
Partners PrEP	181/33,125[2]	204/33,087[2]	0.11 (-0.08, 0.27)	0.5	0.6	0.001 (0.000, 0.002)
TDF2	69/611	43/608	-0.60 (-1.30, -0.11)	11.3	7.1	-0.042 (-0.075, -0.010)
FEM-PrEP	37/1,025	12/1,033	-2.11 (-4.92, -0.63)	3.6	1.2	-0.024 (-0.039, -0.011)
VOICE	6/1,003[3]	9/1,009[3]	0.33 (-0.88, 0.76)	0.6	0.9	0.003 (-0.005, 0.012)

Source: compiled during the evaluation.
Abbreviations: PBO = placebo, RD = risk difference, RRR = relative risk reduction.
[1]Duration of follow-up: iPREX = 324 person-years, Partners PrEP = 7,830 person-years, TDF2 = 1,563 person-years, PROUD = 465 person-years, FEM-PrEP = 1,407 person-years, VOICE = 5,509 person-years.
[2]These numbers represent questionnaires instead of study subjects.
[3]These numbers only represent adverse events of grade 2 or higher.

8 Clinical claim

8.1 The submission described Truvada + SOC as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over SOC. This claim was not strongly supported in terms of the requested PBS listing.

- Truvada + SOC was observed to be significantly more effective than SOC in some of the studies presented by the submission, but this effectiveness was conditional on adherence. As noted above, the applicability of the trial results, including the results of the case control study for highly adherent subjects was unknown.
- Truvada is associated with a range of mild adverse events, such as self-limiting nausea and vomiting.
- Long-term safety of Truvada as PrEP is unknown. Concerns include the long-term impact on bone loss and renal function.
- Safety concerns may exist for subgroups that were not assessed separately (e.g. subjects with high adherence) and subgroups that were largely excluded from clinical trials (e.g. subjects with hepatitis B infection).

8.2 The PBAC noted that the claim of superior comparative effectiveness was not supported by all of the trials. Further, the PBAC considered that it was unclear whether the effect measured in the highly adherent subjects in the iPrEx and Partners PrEP studies would be achieved in the proposed PBS population.

8.3 The PBAC considered that the claim of non-inferior comparative safety was not strongly supported by the available data, given the potential for longer term use of Truvada as PrEP compared to the duration of the studies. However, the PBAC noted that there is experience of longer term use of Truvada being well tolerated in the treatment of HIV, and on balance the safety claim is probably reasonable.

Economic analysis

8.4 The submission presented an economic evaluation using two structurally similar but independent models:

The first was a Markov state transition model which considered the costs and consequences of prevention, detection and treatment of HIV infection in a homogeneous cohort of individuals at high risk of infection. This model considered the costs and consequences of treating an average individual at high risk of HIV infection without taking into account costs and consequences within the broader population.

The second was a population dynamic transmission model, which also considered patterns of PrEP use in the community and the potential impact of the intervention on the Australian HIV epidemic and associated infection risk over time. This model considered the incremental costs and consequences of a given level of Truvada uptake among subjects meeting certain eligibility criteria from within a broader population.

8.5 Although the results of the six trials presented in section B of the submission were meta-analysed, the meta-analysed efficacy estimate was not used in the economic evaluation. Instead, modelled efficacy (RRR 90%) was based on the efficacy in highly adherent subjects (RRR 90%-92%) from two of the six clinical trials (iPrEx and Partners PrEP). The ESC considered that the relevance of these two studies to the intended PBS population was not well supported, in particular given that these studies were undertaken in populations known to have a higher incidence of HIV than Australia. Of the presented studies, the ESC considered that PROUD would appear to be the most (if not only) relevant eligible population.

Table 6: Summary of model structure and rationale

Time horizon	20 years in the model base case versus median ~2 years of use in the trials.	
Outcomes	Costs per QALY gained.	
Methods used to generate results	Model 1 Cohort expected value analysis	Model 2 Monte Carlo simulation
Cycle length	1 month	
Transition probabilities	Model 1 Model entry in susceptible health state. Infection risk: 5% per annum, modified in the Truvada arm based on efficacy, adherence and an inhibition factor. HIV progression and improvement: based on previous Australian modelling, see section D.4.3.3 of the submission. Background mortality: age-specific all-cause mortality sourced from the AIHW GRIM books, 2013. Disease specific mortality: based on literature, see Table D-4 of the submission.	Model 2 Model entry in one of the health states based on epidemiological data (see section D.4.2 of the submission). Infection risk: function of population incidence risk (determined by currently "infectious" population), various individual risk factors, whether or not they take Truvada in that cycle, efficacy, adherence and an inhibition factor. HIV progression and improvement: based on previous Australian modelling, see section D.4.3.3 of the submission. Background mortality: age- and gender-specific all-cause mortality sourced from the ABS 2014. Disease specific mortality: based on literature, see Table D-4 of the submission.
Discount rate	5% for costs and outcomes	
Software package	TreeAge Pro 2015.	

Source: compiled during the evaluation.

Abbreviations: ABS = Australian Bureau of Statistics, AIHW = authoritative information and statistics to promote better health and wellbeing, GRIM = general record of incidence of mortality, QALYs = quality-adjusted life years.

8.6 In model 1, the HIV infection risk was assumed to be a fixed 5% per annum over the whole time horizon (20 years). This risk is higher than the minimum annual risk of HIV infection as required by the proposed PBS listing (3%), which may favour Truvada. Reducing the risk to 3% increased the ICER from $105,000/QALY - $200,000/QALY to more than $200,000/QALY gained. The approach may lack face validity and overestimate the long-term risk of acquiring HIV. For example using a constant risk of 5% results in only 36% of subjects being HIV negative after 20 years in the comparator arm (compared to 80% in the Truvada arm). These proportions of seroconversions were not observed in the clinical trials, which only covered ~2 years e.g. in the iPrEx trial ~5% of placebo subjects and ~3% of Truvada subjects seroconverted.

8.7 The ESC noted that the submission acknowledged that model 2 is an imperfect substitute for the more complex modelling of social and sexual interactions common in the broader HIV literature. However, the submission considered it appropriate for the current decision context "in which the target population is intentionally defined by broad risk criteria, and the evaluation process is constrained in terms of transparency, software and time".

8.8 The ESC noted that the infection rates from model 2 had not been calibrated against Australian HIV infection rates and considered that some of the results generated by model 2 lacked face validity, for instance the rapid decline in incident HIV infections in both the PrEP and the no PrEP scenarios. Annual infections reduced from over 1,000 at baseline to less than 200 in years 7 and 10 in the PrEP and standard of care groups, respectively. The Pre-PBAC Response acknowledged that a rapid decline in annual infections was forecast in both treatment arms, and clarified that the reduction in the standard of care group was "driven by recently implemented initiatives of the National HIV Strategy, the effect of which has yet to be observed." The ESC further noted that the independent NHMRC-funded agent based model developed by researchers at the Kirby institute, UNSW, provided calibrated estimates of the cost-effectiveness of PrEP (Schneider et al, 2014[2]). This model demonstrated that the cost-effectiveness of PrEP is dependent on the extent of targeting by baseline infection risk, but under almost all scenarios modelled PrEP was unlikely to be cost-effective in the Australian context. The ESC considered that an agent based model in which individual interactions, and hence risk over time can be modelled, may be required to accurately model the impact of PrEP.

8.9 The key drivers of the models are provided below.

Table 7: Key drivers of the models

Description	Method/Value	Impact
Time horizon (both models)	20 years; assumed from ~2 years trial duration.	High, favours Truvada
Continuation threshold (model 2)	2%; assumed while the proposed PBS listing does not include continuation criteria.	High, favours Truvada
Individual risk distribution (model 2)	Gamma distribution (mean 1, SD 2.0).	High

Source: compiled during the evaluation.

8.10 Table 8 provides the results of the economic evaluation.

Table 8: Results of the stepped economic evaluation (base case)

Component	Truvada + SOC	SOC	Increment
Model 1			
Costs, undiscounted	$ [redacted]	$91,275	$ [redacted]
QALY, undiscounted	15.7372	15.0422	0.70[1]
Incremental cost/extra QALY gained, undiscounted			$ [redacted]
Incremental cost/extra QALY gained, discounted			$ [redacted]
Model 2			
Costs, undiscounted	$ [redacted]	$ [redacted]	$ [redacted]
QALY, undiscounted	2,561,806	2,556,491	5,315.60
Incremental cost/extra QALY gained, undiscounted			-$28,759
Incremental cost/extra QALY gained, discounted			-$1,143

Source: Tables D-14, D-15, and D-21 pp 167-168 and 176 of the submission.
Abbreviations: SOC = standard of care, QALY = quality-adjusted life year.
[1] In the submission this number was reported to be 0.69, but this seems to be a rounding error.

The redactions in the table show ICERS in the range of $105,000 - $200,000/QALY.

[2] Schneider K, Gray RT, Wilson DP. A cost-effectiveness analysis of HIV preexposure prophylaxis for men who have sex with men in Australia. Clin Infect Dis 2014; 58:1027–34.

8.11 When taking into account the potential impact of Truvada on the broader population, the base case ICER reduces from $105,000/QALY - $200,000/QALY in model 1 to dominant in model 2.

8.12 The PBAC considered that the base case ICER in model 1 was unacceptably high ($105,000/QALY - $200,000/QALY). Decreasing the time horizon in this model to 10 years instead of 20 years further increased the ICER from $$105,000/QALY - $200,000/QALY to over $200,000per QALY gained. Most of the benefits associated with Truvada are expected to accrue beyond the 10 year time horizon. Increasing the risk threshold for access to Truvada reduced the ICER. With a threshold of ≥20% instead of ≥3% annual risk of HIV infection, the ICER reduced from $105,000/QALY - $200,000/QALY to $15,000 - $45,000 per QALY gained.

8.13 In the base case of model 2, Truvada was dominant. Model 2 was sensitive to decreasing the time horizon from 20 to 10 years, which increased the ICER to $75,000 - $105,000per QALY gained. Model 2 was also sensitive to removing the continuation threshold (treatment was discontinued if an individual's risk fell to <2%), which increased the ICER from dominant to $75,000/QALY - $105,000/QALY. This is relevant since the proposed PBS listing does not include continuation criteria. Removing the distribution of the individual risk multiplier increased the ICER from dominant to $75,000/QALY - $105,000per QALY. The skewed risk distribution assumed that a small number of subjects have a very high risk of HIV infection while the majority have a much lower risk than implied by their general demographic characteristics.

8.14 The PBAC noted the advice from ESC and DUSC that model 2 lacked face validity and was considered unlikely to provide a realistic estimate of the true cost effectiveness of subsidising Truvada for PrEP through the PBS. Therefore the PBAC did not accept the submission's base case claim of dominance over SOC.

Drug cost/subject/year: $[redacted].

8.15 The proposed PBS listing suggests 1 tablet per day, ongoing (no maximum duration). The monthly (30-day) Truvada cost is $[redacted]. Assuming 90% adherence, the number of prescriptions required per year is 10.95.

Estimated PBS usage & financial implications

8.16 This submission was considered by DUSC.

8.17 The financial impact analysis presented in the submission takes an epidemiological, prevalence-based approach.

8.18 The forecasted eligible population and uptake of Truvada were based on the results from model 2. Therefore, the financial forecasts are subject to the assumptions of the dynamic transmission model.

8.19 The DUSC considered that the dynamic transmission model used to estimate the eligible population lacked baseline validity and was biased towards underestimating the future need:

- the infection rate was overestimated (5%);

- the estimate of the starting susceptible population of 134,000 persons could not be verified; and
- the rationale for basing the probability of risky behaviour on a gamma distribution was unclear and the bias from this approach was unknown.

8.20 Uptake was assumed to be 80%, applied on a per cycle basis. Adherence was assumed to be 90%, based on the case-control analyses of the iPrex and Partners PrEP studies. MBS costs were the costs for SOC and consistent with the economic model, assuming an MBS cost offset to account for SOC in the control arm.

8.21 The estimated number of prescriptions in the submission was incorrect because adherence was taken into account twice: in calculating the number of prescriptions per subject per year and in calculating the total number of prescriptions per year.

8.22 Table 9 provides the submission's estimated use and financial implications of PBS listing for Truvada as PrEP corrected for the error described above. Based on the information provided in the evaluation, the drug is likely to exceed $20 million/year.

Table 9: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	3,407	6,366	5,298	4,939	3,970
Scripts[1]	37,307	69,708	58,013	54,082	43,472
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	$	$	$	$	$
Net cost to MBS	$1,373,702	$2,566,771	$2,136,154	$1,991,405	$1,600,704
Estimated total net cost					
Net cost to PBS/RPBS/MBS	$	$	$	$	$

Source: Table E-9, p. 191 of the submission.
These numbers where adapted in order to correct for taking adherence into account twice.
[1]Assuming 10.95 scripts per year as estimated by the submission.

The redactions in the table show that, at Year 5, the net cost to the PBS/RPBS/MBS would be $30 - $60 million per year.

8.23 DUSC estimated that the upper limit of the eligible population could be over 20,000 persons. However, there were difficulties in estimating the treated population as there are several PrEP demonstration projects involving treatment with Truvada and generic versions of this combination therapy running in NSW, Victoria and Queensland with a large number of enrolments. There could be a large primed market who may move to PBS subsidised Truvada.

8.24 DUSC considered the number of prescriptions per patient could be less than estimated by the submission. Preliminary results from the VicPrEP demonstration project suggest that participants were adherent at least 4 of 7 days per week. DUSC noted that the use of tenofovir disoproxil fumarate and emtricitabine as on demand pre-exposure prophylaxis before and after sexual activity was being investigated.[3]

[3] J.-M. Molina, C. Capitant, B. Spire et al. (2015) On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. N Engl J Med 373:2237-46.

8.25 The reduction in use of ART to treat avoided cases of HIV was calculated in a supplementary analysis in section E.8 of the submission. Assuming an ART cost of $1,121 per patient per month, the estimated savings to the PBS were $10 - $20 million in years 1 to 5.

8.26 DUSC advised there may be substantial risk of use in the medium risk population. The following factors may contribute:
- The lack of an Australian risk calculator to identify which subjects are eligible.
- The lack of auditable risk criteria.
- The Australian PrEP guidelines advice considering PrEP in subjects with medium risk, while the proposed listing is for 'substantial risk'. It was uncertain whether 'substantial risk' is equivalent to high risk.
- The absence of any requirements regarding stopping Truvada when individual risk falls below 3% (or 2% as assumed in the economic evaluation).

8.27 In the base case, the submission calculated an MBS cost offset based on the assumption that high risk subjects who do not take Truvada would be expected to undergo the recommended twice annual HIV and STI screenings. This cost-offset may be overestimated since subjects are currently tested on average less than twice per year. Completely removing the MBS cost offset from the calculations increases the cost to government by 5.24%.

Quality Use of Medicines

8.28 The submission proposed that in order to receive Truvada, subjects must be enrolled in an approved PrEP service where they would receive information about safe sex practices, monitoring of adverse events (including renal monitoring) and 3-monthly HIV and STI tests. The use of Truvada may lead to viral resistance in subjects with unrecognised HIV-1 infection (see TGA Clinical Evaluation Report).

8.29 The DUSC considered that there is a high risk of non-adherence as the target population would be mainly young and otherwise healthy individuals with no regular medication taking behaviours established. The provision of adherence support was not adequately addressed by the submission, in particular the strategies that would be used by PrEP services to achieve this. Such considerations include the support given at the first repeat, the involvement of pharmacists and whether active recall procedures (eg where patients who do not return for a repeat appointment or prescription are actively followed up by the PrEP service) would be employed.

8.30 DUSC noted that there were indications of less condom use over time in follow-up studies, including the Partners PrEP Study and early data from the VicPrEP demonstration project. DUSC considered that there was the potential for Truvada to replace safe sex practices.

8.31 DUSC noted that there was a lack of long-term data on bone toxicity after extended use of Truvada for PrEP. DUSC noted that as a condition of registration the Advisory Committee on Prescription Medicines (ACPM) proposed that the sponsor contribute to the Kirby Institute surveillance of PrEP and monitor PrEP failures and drug resistance.

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

9 PBAC Outcome

9.1 The PBAC rejected the request for PBS listing on the basis of unacceptable and uncertain cost effectiveness in the proposed population and at the proposed price. The PBAC noted that the submission had tried to limit the population that would be eligible for treatment to those at highest risk, which represented a relatively small proportion of the potential population. The PBAC noted this restriction was proposed in order to improve the cost-effectiveness rather than to limit use in those who would not benefit. However, the PBAC considered that the cost-effectiveness estimates were unreliable and that attempts to severely restrict the eligible population based on individual risk calculation may not be feasible, appropriate or acceptable to clinicians and consumers. The PBAC considered it may be more appropriate for a broader group of individuals to have access to Truvada as PrEP, for example all MSM for whom clinician and consumer judge the potential benefit to outweigh the risk. The PBAC noted that in order to make Truvada available for PrEP to the whole 'at risk' population a substantial reduction in price would be needed to achieve cost effectiveness.

9.2 In making its decision the PBAC noted that, based on the evidence provided, pre-exposure prophylaxis could reduce the risk of acquiring HIV when used in combination with safer sex practices and regular HIV testing, but as a strategy PrEP was not always effective in preventing the acquisition of the virus. The PBAC noted that the efficacy of Truvada was highly dependent on adherence. Likely adherence in the PBS population is unknown, but 'real life' adherence is generally accepted to be lower than what is observed in clinical trials. It is not clear if subjects at high risk of contracting HIV due to self-reported low adherence to safer sex practices would also have lower adherence to medication.

9.3 The PBAC agreed with the ESC that it was difficult to make a reliable estimate of the effectiveness and cost-effectiveness of Truvada for PrEP given that key details regarding the proposed listing remain unclear, including:

- how Truvada would be used in clinical practice, including whether/when subjects would cease treatment and the possibility of intermittent rather than daily use. It was noted that studies are both published and underway using alternative regimens to that proposed in the submission; and
- the infrastructure that would be required to support 'approved PrEP services' to ensure effective use of Truvada.

9.4 Overall, the PBAC considered that the available data were not representative of the proposed PBS population. The Committee's concerns about the applicability of the trial data to the Australian setting included that a large proportion of the data were generated in communities known to have a substantially higher incidence of HIV infection (and therefore higher risk) than the Australian population. The PBAC also noted that the trials assessed the efficacy of Truvada together with encouragement of safe sex practices and it is unknown if safe sex practices would be utilised to the same extent in the Australian population, and how this would change over time. The PBAC noted that reduced condom use had been reported with the Vic PrEP and PrELUDE Australian PrEP demonstration studies. The impact of these differences on the effectiveness of Truvada in clinical practice is unclear.

9.5 The PBAC noted that Australian data are currently being collected, including from the PrEP demonstration studies being run in several of the states, but noted that these studies are uncontrolled and may include individuals at lower risk than the proposed PBS population. It remained unclear whether the results would be generalisable to the proposed PBS population.

9.6 The PBAC agreed that based on the studies presented there is evidence that the use of Truvada as PrEP appears to be effective in reducing the transmission of HIV in some circumstances. The extent to which these results would be realised in the clinical setting was unclear, given the applicability concerns.

9.7 The PBAC considered that the economic models presented were unlikely to provide a reliable estimate of the true cost effectiveness of Truvada in the requested population. The base case ICER estimated by model 1 ($105,000/QALY – $200,000/QALY) was unacceptably high and uncertain. The dominant ICER estimated by model 2 was unlikely to be realised. Issues with economic models included:

Both models likely overestimated the efficacy of Truvada:

- The models assumed 90% adherence in clinical practice (continuously) and for adherent subjects a relative risk reduction of 90% was assumed, based on the case control analyses presented in the submission.
- The potential impact of Truvada on adherence to other preventative strategies was not considered in the model in the base case.

In model 1, using a constant risk of 5% it was predicted that without PrEP, 64% of the eligible population would be HIV positive after 20 years. This lacks face validity. Reducing the risk to 3% increased the ICER from $105,000/QALY – $200,000/QALY to more than $200,000per QALY gained.

In model 2:

- Sexual contact between individuals was assumed to be random rather than assortative by risk level. This was considered unrealistic as individuals at high risk may be more likely to have contact with other high risk individuals rather than someone who is low risk. The model population was closed and hence does not allow new at-risk MSM to enter, allowing for transmission to be rapidly exhausted even in the no PrEP scenario.
- The model assumed high uptake of Truvada as PrEP in high risk individuals, which the PBAC considered was not reasonable since high risk patients are partly defined by low uptake of currently available ‘safe sex’ practices (eg condoms).
- The PBAC noted the agent based model developed by researchers at the Kirby Institute, in which individual interactions are represented over time. The PBAC noted that the results of this model suggest the price of Truvada has a strong influence on cost-effectiveness of PrEP, with the current PBS list price of Truvada only likely to be cost-effective for PrEP when used in men in a regular partnership with an HIV-discordant man.
- The ICER was sensitive to a range of input parameters including treatment adherence, the risk level at which individuals discontinue treatment, the distribution of risk across the population and the model time horizon.

9.8 The PBAC agreed with the DUSC that the dynamic transmission model used to estimate the eligible population lacked face validity and was biased towards underestimating the future need.

9.9 The PBAC considered a major re-submission would be required which considered the following:

- The population eligible for treatment, noting the PBAC considered it would be more appropriate for a broader group of individuals with potential benefit to have access to Truvada as PrEP;
- The appropriate and likely use in clinical practice, including the possibility of intermittent use;
- Details relating to the 'approved PrEP service';
- Adherence with Truvada as PrEP, and the potential impact of Truvada on other preventative strategies, in clinical practice;
- The issues with the economic models as outlined in paragraph 7.7, and hence the cost-effectiveness of Truvada as PrEP; and
- The size of the eligible patient population likely to seek access.

9.10 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

10 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.

11 Sponsor's Comment

The submission sought a listing consistent with the TGA indication, using the World Health Organization (WHO) recommendation for PrEP suitability to identify the eligible population, but notes the PBAC's considerations regarding defining the eligible population. The Sponsor is committed to working with the PBAC towards the future listing of Truvada for PrEP.