

An addendum to this Public Summary Document (PSD) has been included at the end of the document.

5.03 CABOTEGRAVIR, Suspension for injection, 600 mg in 3 mL, Apretude[®], ViiV HEALTHCARE PTY LTD.

1 Purpose of Submission

- 1.1 The Category 2 submission requested a General Schedule, Authority Required (STREAMLINED) listing for cabotegravir long-acting injection (CAB-LA) for use as pre-exposure prophylaxis (PrEP) for human immunodeficiency virus-1 (HIV) infection in persons in whom tenofovir disoproxil and emtricitabine (TD/FTC) is contraindicated, or persons who are intolerant or have reported of suboptimal adherence to TD/FTC.
- 1.2 Listing was requested on the basis of a cost-utility analysis versus placebo, or standard of care (SoC) alone.

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

Component	Description
Population	Persons at risk of HIV infection unable to be treated with oral PrEP (TD/FTC), due to contraindication, intolerance or repeated reporting of suboptimal adherence.
Intervention	Cabotegravir long-acting injection in combination with standard of care safer sex practices. <ul style="list-style-type: none"> Initiation injections: Single 600 mg (3 mL) injections administered intramuscularly (gluteal) one month apart for two consecutive months. Continuation injections: A single 600 mg (3 mL) injection administered intramuscularly (gluteal) every two months.
Comparator	Placebo (as proxy for no medical PrEP) in combination with standard of care safer sex practices
Outcomes	HIV infection; safety.
Clinical claim	In individuals at risk of HIV infection and unable to be treated with TD/FTC, CAB-LA reduces the risk of HIV infection and has an acceptable and manageable safety profile compared to no intervention.

Source: Table 1, p 2 of the submission.

CAB-LA = cabotegravir long-acting injection; HIV = human immunodeficiency virus; PrEP = pre-exposure prophylaxis; TD/FTC = tenofovir disoproxil and emtricitabine

2 Background

Registration Status

- 2.1 CAB-LA (as well as CAB film - coated tablets) was TGA registered for use in the PrEP setting on 9 August 2022 under the following indication:
- In at-risk adults and adolescents (at least 12 years of age) and weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection;

- Tablets may be used as an oral lead-in to assess tolerability of cabotegravir prior to administration of cabotegravir injections or as short-term oral PrEP in individuals who will miss planned dosing with cabotegravir injections; and
- Individuals must have a documented negative HIV-1 test prior to initiating CAB-LA for HIV-1 PrEP.

3 Requested Listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
CABOTEGRAVIR					
Cabotegravir 600 mg/3 mL prolonged-release suspension for injection	\$1,405.89 published price \$█ effective price	1	1	0	Apretude

Category / Program: Section 85 - General Schedule
Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED)
Clinical criteria:
The treatment must be the sole PBS-subsidised therapy for this PBS indication.
AND
Clinical criteria:
Patient must have at least one of the following prior to having the latest PBS-subsidised prescription issued: (iii) A negative HIV test result no older than 8 weeks, (iv) Evidence that an HIV test has been conducted, but the result is still forthcoming,
AND
Clinical criteria:
Patient must be contraindicated or intolerant to treatment with tenofovir disoproxil and emtricitabine at the time of initiation with this drug,
OR
Clinical criteria:
Patient must have repeatedly reported adherence to tenofovir disoproxil and emtricitabine as PrEP that is sufficiently suboptimal to compromise both efficacy and patient safety at the time of initiation with this drug.
Notes: PrEP users who explain they have had suboptimal adherence but are willing and suitable to continue on tenofovir disoproxil and emtricitabine as PrEP, should be offered additional adherence education. It is advised that individuals have a documented negative HIV-1 result immediately prior to initiating this drug and undergo repeat HIV-1 testing at regular intervals while on this drug for this indication, in accordance with applicable guidelines. Special Pricing Arrangements apply.

Source: Table 9, pp33-34 of the submission.

- 3.1 The submission requested an effective dispensed price for maximum quantity (DPMQ) of \$█ compared to the existing DPMQ of CAB with rilpivirine (RPV) for HIV infection of \$█ for a pack containing 1 vial CAB 600 mg in 3 mL and 1 vial RPV 900 mg in 3 mL.
- 3.2 The submission noted that currently, a prescription for oral PrEP provides up to 90 days of TD/FTC supply (30 tablets; two repeats) at a time, which aligns with the Australian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) recommendations for clinical reviews and HIV testing to be undertaken at least three

monthly. However, the proposed duration of therapy per prescription for CAB-LA was shorter than currently permitted for oral PrEP due to the two-monthly dosing regimen of CAB-LA during the continuation phase. The submission proposes that the frequency of review will be every two months for CAB-LA as extending the frequency of clinical reviews and HIV testing to 4-monthly will not comply with the current edition of the ASHM guidelines. As is the case for prescribing oral PrEP currently, it is expected individuals will be counselled on the requirement for these bi-monthly visits when determining whether CAB-LA is appropriate for them. The submission recognised that prescribing recommendations in future ASHM guidelines may advise alternative dosing frequency. The ESC noted bi-monthly visits to receive CAB-LA injections would lead to an increase in clinic visits and HIV testing and also noted that the ASHM Guidelines, regarding time between sexual health consultations, had not been updated (at the time of ESC advice) to consider optimal health care provider engagement for individuals using CAB-LA for PrEP.

- 3.3 The submission did not seek a separate listing for the optional oral lead-in or for missed doses for CAB-LA. The submission considered that utilisation of the oral lead-in would be low, but the sponsor was nevertheless willing to provide 'direct access' to CAB tablets on an as needed basis. No details on how this supply would be managed in practice was provided in the submission or if there would be limitations to the quantity of tablets allowed. For example, in the pivotal HPTN-083 trial, one participant was in the oral lead-in phase for 115 days. This may represent a potential source of inequity of access particularly in the case of missed doses. No details on the potential price charged for non-PBS-subsidised access to oral cabotegravir was provided. Cabotegravir tablets are currently listed on the PBS as a \$100 HSD (Community Access), streamlined authority at a higher price than the cost-effective price for oral PrEP (i.e. cost minimised to dolutegravir and other integrase inhibitor (INSTIs)).
- 3.4 The ESC noted that the requested restriction was narrower than the TGA indication as the requested restriction specifies a 'second line' population defined as individuals who were willing to take PrEP but were contraindicated to, were unable to tolerate, or were unable to adhere to an effective regimen of TD/FTC. The submission acknowledged that CAB-LA would be a suitable option for all individuals at risk of HIV infection for PrEP. However, the submission claimed that due to the relatively low cost of TD/FTC on the PBS and that TD/FTC has been shown to be a highly effective HIV prevention strategy when used optimally, listing of CAB-LA for individuals otherwise eligible for oral PrEP would not be feasible. The Pre-Sub-Committee Response (PSCR) stated that the proposed clinical place was reasonable, as the target population comprises of individuals at risk of HIV infection who are unable to use oral PrEP and argued that the clinical place of CAB-LA proposed in the submission was validated through discussions with local clinicians and key opinion leaders, and is consistent with

an expert discussion paper from the Kirby Institute (Bavinton 2022¹) as well as International guidelines (CDC 2021²).

- 3.5 The ESC considered that while the clinical need for alternative PrEP options is high in individuals for whom oral PrEP is not a viable option, it also considered the dose regimen and longer dose interval, as well as the potential for CAB-LA to be clinically superior to TD/FTC (although it considered this claim uncertain in the Australian setting) would make it an effective and appealing option for a broad population seeking to use PrEP. On that basis, the ESC expressed a preference that CAB-LA should be available for a broader population than proposed in the submission.
- 3.6 The Pre-PBAC Response acknowledged CAB may be a suitable option for all patients at risk of HIV infection, including those who would otherwise be eligible for TD/FTC, consistent with the clinical evidence base for CAB in PrEP. However, the Response also stated the substantial drop in price for TD/FTC since listing in 2018 meant listing on a cost minimisation basis with TD/FTC in a broader population was not commercially viable. On that basis, the Response argued the approach taken in the submission was to maximise attainable health outcomes by targeting a subset of the population at risk of HIV infection who cannot use oral PrEP and have a high clinical need for a new PrEP treatment modality.
- 3.7 Based on the requested restriction, individuals who are contraindicated to TD/FTC on the basis of renal insufficiency meet the objective clinical criteria (CrCL < 60mL/min). However, the evaluation considered that contrary to the submission's claims, age (less than 18 years) may not be a reasonable contraindication to TD/FTC treatment as PBS listings for TD/FTC are not currently restricted by age. Additionally, ASHM guidelines note that TD/FTC is FDA approved for PrEP in adolescents.
- 3.8 Based on the submission's financial estimates, it is expected that contraindicated individuals make up a small percentage of the eligible population (3-6%). Most individuals were assumed by the submission to be eligible for CAB-LA on the basis of being unable to tolerate or have sub-optimal adherence to TD/FTC. These were more subjective criteria and there was a high risk of individuals who would otherwise benefit from less expensive prophylaxis with TD/FTC accessing CAB-LA instead. This would potentially lead to a higher cost to government for a much lower incremental benefit (if any) than presented in the submission and may not represent a cost-effective treatment under the proposed restriction. The PSCR acknowledged the proposed restriction criteria for determining eligibility in terms of intolerance or suboptimal adherence to oral PrEP may be open to subjective interpretation, however argued the

¹ Bavinton BR, Bushby B, Murphy D, Cornelisse VJ, Philpot S, Chan C, Wright EJ, Grulich AE. Discussion Paper: Research priorities for implementing long-acting injectable Cabotegravir for PrEP in Australia. Sydney: Kirby Institute, UNSW Sydney; 2022.

² Centers for Disease Control and Prevention: US Public Health Service: Preexposure prophylaxis for the prevention of HIV infection in the United States—2021 Update: a clinical practice guideline. <https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf>.

wording of the restriction included statements such as the requirement to report ‘repeated’ issues prior to discontinuing oral PrEP prescribing, which was consistent with the ASHM 2021 guidelines. The PSCR provided a proposal for a Risk Sharing Arrangement (RSA) to address the risk of use in a broader population (see ‘Financial Management – Risk Sharing Arrangements’).

- 3.9 As CAB-LA represents a new treatment modality for HIV PrEP and consistent with the current listing of CAB-LA (in combination with rilpivirine) for the treatment of HIV, the submission considered an Authority Required (STREAMLINED) listing was an appropriate authority level. Alternatively, the submission noted that a Restricted Benefit listing for CAB-LA would align with the current PBS listings of TD/FTC as HIV PrEP.

For more detail on PBAC’s view, see section 7 PBAC Outcome.

4 Population and Disease

- 4.1 Infection with HIV can result in an acute illness and chronic sequelae, including but not limited to acquired immunodeficiency syndrome (AIDS). HIV is spread through infected blood, semen or vaginal fluids. Treatment with antiretroviral therapies (ART) is recommended for HIV-infected individuals to reduce morbidity and mortality (including AIDS related morbidity and mortality). Treatment with ART is typically for life (or until all ART options have been exhausted) and can impact on quality of life and mortality.
- 4.2 Currently TD/FTC is the only PBS-listed medicine for HIV PrEP. CAB-LA is proposed for PBS listing in individuals who are contraindicated TD/FTC.
- 4.3 CAB is an integrase strand transfer inhibitor (INSTI). It inhibits HIV integrase by binding to the integrase-active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration, which is essential for the HIV replication cycle.

For more detail on PBAC’s view, see section 7 PBAC Outcome.

5 Comparator

- 5.1 The submission stated that the population targeted for CAB-LA on the PBS comprises of individuals at risk of HIV infection who are unable to use oral HIV PrEP. The submission considered that as there is no medical PrEP alternative for these individuals, the nominated comparator is placebo (as a proxy for no PrEP) + overall SoC HIV infection prevention strategy. The comparator is referred to as SoC from herein.
- 5.2 The submission noted that SoC may include regular testing for HIV infection and other sexually transmitted infections, as well as condom use.
- 5.3 The submission acknowledged that CAB-LA would be a suitable option for all individuals at risk of HIV infection, i.e., including individuals who are otherwise eligible

for oral PrEP, thus offering individuals the choice between oral and injectable PrEP modalities. This is consistent with the populations enrolled in the pivotal HPTN-083 and HPTN-084 trials of CAB-LA and the TGA-approved indication but not with the proposed restriction. The submission claimed that due to the relatively low cost of TD/FTC on the PBS listing of CAB-LA for individuals otherwise eligible for oral PrEP would not be feasible.

- 5.4 Overall, SoC was the appropriate comparator in individuals who have a medical contraindication to TD/FTC. However, in individuals with suboptimal adherence or tolerance issues, TD/FTC may still be prescribed to these individuals (e.g. the ASHM guidelines recommend on-demand PrEP as an option for cis-gender men who have sex with men (MSM) who may have side effects from daily PrEP)^{3,4} and therefore TD/FTC would be the medicine most likely to be replaced and would be the comparator. In the financial estimates presented by the submission, it was estimated that only between 3 and 6% of eligible individuals would be contraindicated to TD/FTC, with the majority (94-97%) of individuals classified as having suboptimal adherence. As such, it may be argued that TD/FTC should be the comparator even in the proposed population, or a weighted comparator may be more appropriate. While the data provided in the submission includes a direct comparison of CAB-LA with TD/FTC as PrEP (but not in the proposed 'second line' setting), no information on the relative cost-effectiveness was provided.
- 5.5 The ESC considered SoC to be a reasonable comparator in a population for whom TD/FTC is not a viable option, however considered including those who have suboptimal adherence to oral PrEP in this population introduced substantial uncertainty as this definition was subjective and such a population would be difficult to quantify. The ESC considered that re-trialling oral PrEP or sub-optimally effective PrEP could potentially be considered a relevant comparator for the cohort proposed to be eligible due to suboptimal adherence.
- 5.6 The Pre-PBAC Response argued that the proposed clinical place of therapy for CAB-LA is for patients in whom oral PrEP is not a viable option, including those who have discontinued oral PrEP due to repeatedly reported suboptimal adherence. As there is no medical PrEP alternative for these patients who have discontinued oral PrEP, the Response argued that SoC is the most appropriate comparator for CAB-LA in this setting.
- 5.7 In the context of a comparison against TD/FTC, the PBAC previously recommended a price premium to a long-acting injectable option in the HIV positive setting.

³ ASHM (2019) 'National PrEP guidelines, Improving medication adherence'
<https://prepguidelines.com.au/Files/10-improving-adherence.pdf>

⁴ ASHM, 'PrEP dosing regimens' <https://ashm.org.au/wp-content/uploads/2022/04/PrEP-dosing-guide-August-2020.pdf>

Specifically, in the consideration of CAB + RPV LA injection in the HIV treatment context at the November 2021 PBAC meeting, the PBAC had concluded the following:

- ‘While recognising that the availability of a long-acting injectable option for the management of HIV is likely to offer some QoL and adherence benefits for a small number of patients...the extent of benefit was difficult to quantify...However, based on the input from consumers and clinicians and the sponsor hearing in support of the submission, the PBAC considered that on the basis of potential health benefits from likely improved adherence and improved QoL for a small number of PLHIV, a price advantage ... over the least costly relevant alternative (Dovato[®], dolutegravir/lamivudine) would be acceptable.’ (November 2021 PBAC Meeting, paragraph 7.10).

5.8 The submission presented other rationales for listing that do not strictly fit into typical PBAC decision making. Some of these rationales have been synthesised during the evaluation in Table 2.

Table 2: Key auxiliary arguments and rationales to listing CAB-LA on the PBS provided in the submission.

Argument / Rationale	Comment
The chief goal of Australian health policy on HIV is the ‘virtual’ elimination of transmission within the country (AFAO, 2021; DoH 2018). Maximising the use of HIV PrEP among individuals at risk of acquiring HIV is considered a key component in achieving this goal, with the intent that 95% of people for whom PrEP is beneficial use it by 2025 (AFAO, 2021). The availability of CAB-LA on the PBS would address a high clinical need for an alternative medical PrEP for patients at risk of HIV and willing to use PrEP but unsuitable for oral PrEP. This will accelerate progress towards greater PrEP utilisation and coverage, which has the potential to help prevent new local cases of HIV acquisition and advance Australia towards achieving its target of virtual elimination of HIV transmission.	This is a highly relevant argument. It would be reasonable to assume that an additional PrEP regimen could increase uptake of PrEP in general and help meet Australian health policy goals. However, there are no clear estimates of the magnitude of the uptake benefit of listing CAB-LA.
The submission noted that during the evaluation of TD/FTC for HIV PrEP, the PBAC advised that maximum price it would consider to be acceptably cost-effective, noting the price and incremental cost-effectiveness ratios (ICERs) of other large population preventive interventions such as lipid lowering medicines and vaccines on the National Immunisation Program (NIP) would be an annual treatment cost of \$2,500 per patient per year. This is equivalent to a DPMQ of approximately \$205 per pack of 30 tablets’ (paragraph 5.2, TD/FTC PSD, December 2017). The submission argued that this effectively demonstrates the willingness to pay for a new therapy for HIV PrEP.	While this may be an informative benchmark, applying the willingness to pay for another submission for a first in class treatment to this submission may not be reasonable. Additionally, it should be noted that CAB-LA does not meet this threshold. The proposed annual cost of ongoing treatment with CAB-LA (excluding the additional dose in year 1) at the DPMQ level was approximately \$■■■■, which was ■■■% greater than the price considered as cost-effective for PrEP in December 2017.

Source: pp1-35 of the submission.

AFAO = Australian Federation of AIDS Organisations; CAB-LA = cabotegravir long-acting injection; DoH = Department of Health; DPMQ = dispensed price per maximum quantity; HIV = human immunodeficiency virus; PrEP = pre-exposure prophylaxis; PSD = public summary document; TD/FTC = Tenofovir disoproxil / emtricitabine;

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 information presented from two members of the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) PrEP guidelines committee discussed the draft guidelines on CAB-LA as PrEP, which state its suitability as an option for people will depend on a range of factors including:

- A person's HIV infection risk;
- Current HIV negative status;
- Medical contraindication to TD/FTC (noting tenofovir alafenamide (TAF) based oral PrEP is not PBS subsidised but may be suitable for some of people);
- Prior experience and poor adherence to oral PrEP;
- Whether a person is PrEP naïve;
- A clinician's assessment that individual circumstances such as medical history, mental health and/or psychosocial factors mean they would be at risk of HIV acquisition if they were not provided with CAB-LA;
- People who report they are highly unlikely to be able to adhere to oral PrEP for a range of factors including difficulty remembering to take tablets, concerns around confidentiality and safety around needing to store PrEP tablets etc.;
- Whether a person's life circumstances can incorporate the logistics of using CAB-LA for PrEP, bearing in mind the requirement to attend appointments at strict 8 week intervals, given the risk that unplanned missed visits may lead to CAB-LA resistance if HIV is acquired when sub-therapeutic levels of CAB-LA are present in the bloodstream;
- A person's understanding of the long pharmacokinetic tail of CAB-LA and the requirement to use another form of PrEP for at least 12 months after ceasing CAB-LA treatment to reduce the risk of resistance developing if they acquire HIV in this time; and
- Willingness to have injections, which can be associated with injection site reactions.

6.2 The hearing expressed the view that the draft guidelines balance individual clinical and population-level prevention needs and the fact oral PrEP will remain significantly cheaper than injectable PrEP, at least in the near future. The hearing also discussed the successes of PrEP accessibility in Australia and the decline in new HIV diagnoses with the increasing availability and affordability of oral PrEP, and highlighted the need for alternative forms of PrEP to ensure Australia can achieve its strategy goal of the virtual elimination of the transmission of HIV.

Consumer Comments

- 6.3 The PBAC noted and welcomed the input from individuals (6), health care professionals (6) and organisations (4) via the Consumer Comments facility on the PBS website. The comments from individuals noted some concern regarding the long term safety of both CAB-LA and TD/FTC but suggested the benefits outweigh the risks, and highlighted the need for alternative options to a daily medication, particularly for those who could not adhere to or use TD/FTC. The comments from health professionals also highlighted the lack of treatment options for those who cannot use TD/FTC or struggle with adhering to an oral PrEP regimen for various reasons, including the potential stigma and privacy concerns with keeping supply of a therapy with a known medical purpose in the community, however also noted the long pharmacokinetic tail of injectable CAB necessitated appropriate clinical management of people who experience seroconversion to avoid the development of drug resistance.
- 6.4 The PBAC noted the advice received from the West Australian AIDS Council (WAAC), Thorne Harbour Health (THH), the Australian Federation of AIDS Organisations (AFAO)/National Association of People with HIV Australia (NAPHWA) (combined submission) and ACON Health discussing the current context of PrEP use in Australia, the challenges with the current oral TD/FTC option and importance of additional options for people using or seeking to use PrEP effectively. The comments from the organisations included:
- The WAAC outlined the benefits of being able to offer a PrEP option that is suitable for people who cannot use TD/FTC and is longer acting and doesn't require daily or episodic dosing, and stated many people they see live chaotic lives, including homelessness, isolation, drug and alcohol use, intimate partner violence, mental illness etc. which complicate being able to adhere to oral PrEP dosing requirements.
 - THH made similar comments to the WAAC and also stated that more options will lead to better PrEP coverage for individuals, resulting in fewer HIV transmissions as different people will use the options that best suit their needs. In addition, THH also noted the need for CAB-LA to be administered by a health professional at relatively precise intervals, which would likely lead to an increase in time spent at the doctor at set times, which may make it more inconvenient for some people. The THH also highlighted the long pharmacokinetic tail of injectable CAB-LA meant it was recommended people continue to use oral PrEP for a year after stopping injectable medication to reduce the risk of resistance developing if a person was exposed to HIV infection in that time.
 - The AFAO and NAPHWA discussed the Australian context of high PrEP use in the MSM population and the vital role of PrEP in achieving the goal of virtual elimination of HIV transmission by 2030. The comments also described that the listing of injectable CAB-LA is important for people who cannot take TD/FTC due

to contraindication or tolerability issues and for those who experience factors that limit a person's ability to maintain a regular drug regimen, including frequent travellers (including fly-in, fly-out workers), people who are homeless or in custodial settings, and those who have privacy challenges or experience sexuality-related stigma.

- ACON Health expressed similar views to the other organisations' comments, however also noted barriers identified in the NSW HIV strategy 2021-2025 included unwillingness to take medication to prevent HIV, fear of side effects, education level or income, low health literacy, Medicare ineligibility and difficulties finding non-judgemental clinical care. ACON Health highlighted that having alternative forms of biomedical PrEP alongside other health system measures, such as continuing education, health promotion and targeted interventions for priority populations, were required to achieve the virtual elimination of HIV transmission by 2030.

Clinical Trials

6.5 The submission was based on two head to head randomised trials comparing CAB-LA with TD/FTC in the HIV PrEP population (HPTN-083 and HPTN-084) as well as an indirect comparison informed by the HPTN-083 trial and two trials comparing TD/FTC with placebo (as a proxy for SoC) (iPrEx, and IPERGAY) and one trial comparing TD/FTC either immediately or after a deferral period of one year (PROUD) to estimate the effect of CAB-LA versus SoC via the common comparator of oral TD/FTC. The submission assumed that the deferral cohort in PROUD would be reflective of the SoC population. The included trials are as follows:

- HPTN-083 (N = 4,570): a multi-centre, double blind randomised placebo controlled non-inferior study in HIV uninfected cisgender men and transgender women who have sex with men (MSM and transgender women [TGW]) comparing CAB-LA (with an oral tablet lead-in phase) versus oral TD/FTC;
- HPTN-084 (N=3,224): double-blind, two-arm, randomised (1:1), placebo-controlled superiority study of the safety and efficacy of CAB-LA (with an oral tablet lead-in phase) compared to daily oral TD/FTC for HIV prevention in sexually active HIV uninfected women at risk of HIV;
- iPrEx (N=2,499): a randomised double-blind trial of once daily oral TD/FTC versus placebo in MSM and TGW at high risk of HIV;
- PROUD (N=544): a randomised, open label trial of once daily oral TD/FTC either immediately or after deferral period of one year in Gay, bisexual and other MSM at high risk of HIV; and
- IPERGAY (N=414) a randomised double-blind trial of sexual activity dependent oral TD/FTC or placebo in MSM at least 18 years of age at high risk of HIV infection. It

appeared that the sexual activity dependent oral TD/FTC was consistent with ‘On Demand’ PrEP use in the Australian setting.

6.6 Details of the trials presented in the submission are provided in Table 3.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
HPTN-083 NCT02720094	A Phase IIb/III Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/ Emtricitabine (TDF/FTC), For Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women who have Sex with Men Landovitz, R. J., et al. Cabotegravir for HIV prevention in cisgender men and transgender women Hanscom, B. S., et al. Evaluating group-sequential non-inferiority clinical trials following interim stopping: The HIV Prevention Trials Network 083 trial. Grinsztejn, B., et al. HPTN 083 interim results: efficacy of pre-exposure prophylaxis (PrEP) containing long-acting injectable cabotegravir (CAB-LA) is maintained across regions and key populations. Landovitz, R. J., et al. HPTN083 interim results: pre-exposure prophylaxis (PrEP) containing long-acting injectable cabotegravir (CAB-LA) is safe and highly effective for cisgender men and transgender women who have sex with men (MSM, TGW). Landovitz, R. J., et al. UPDATED EFFICACY, SAFETY, and CASE STUDIES in HPTN 083: CAB-LA VS TDF/FTC for PrEP.	CSR. March 2021 NEJM 2021;385(7): 595-608. Clinical Trials 2022; 19(6): 605-612. Journal of the International AIDS Society 2020; 23(SUPPL 4). [abstract] Journal of the International AIDS Society 2020; 23(SUPPL 4). [abstract] Topics in Antiviral Medicine 2022; 30(1 SUPPL): 37. [abstract]
HPTN-084 NCT03164564	A Phase 3 Double Blind Safety and Efficacy Study of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women (HPTN 084) Delany-Moretlwe, S., et al. Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial. Delany-Moretlwe, S., et al. Long acting injectable cabotegravir is safe and effective in preventing HIV infection in cisgender women: Interim results from HPTN 084. Delany-Moretlwe, S., et al. EVALUATION of CAB-LA SAFETY and PK in PREGNANT WOMEN in the BLINDED PHASE of HPTN 084. Moore, M., et al. Estimated long-acting PrEP effectiveness in the HPTN 084 cohort using a model-based HIV incidence in the absence of PrEP	CSR. June 2021 The Lancet 2022; 399(10337): 1779-1789. Journal of the International AIDS Society 2021; 24(SUPPL 1): 8. [abstract] Topics in Antiviral Medicine 30 2022;(1 SUPPL): 278. [abstract] Journal of the International AIDS Society 2021' 24(SUPPL 4). [abstract]
Tenofovir disoproxil emtricitabine versus trials		
iPrEx NCT00458393	Anderson, P. L., et al. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. Grant RM, Lama JR, Anderson PL, McMahon BS, et al. Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men. Moon, K. T. Reducing HIV transmission via preexposure prophylaxis with antiretroviral drugs.	<i>Science Translational Medicine</i> 2012; 4(151). <i>NEJM</i> 2010; 363:2587-2599. <i>American Family Physician</i> 2011; 84(10): 1169-1175.
PROUD NCT02065986	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.	<i>The Lancet</i> 2016; 387 (10013):53-60.
IPERGAY NCT01473472	Molina, J. M. et al. IPERGAY Study Group. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. Molina, J. M., et al. On demand PrEP with oral TDF-FTC in MSM: Results of the ANRS ipergay trial.	NEJM, 2015; 373(23), 2237–2246 Topics in Antiviral Medicine, 2015; 23: 10. [abstract]

Source: Table 13, pp41-43 of the submission and Table 2, p10 of Appendix 1 to the submission.

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

Table 4: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Population	Outcomes	Use in modelled evaluation
CAB-LA versus SoC						
HPTN-083	4,570	R, DB 48 weeks	Low	MSM & TGW at risk of HIV (United States, Peru, Brazil, Argentina, Thailand, Vietnam, and South Africa)	HIV incidence	Comparative HIV incidence was applied to an indirect comparison against SoC, which was used in the economic evaluation.
HPTN-084	3,224	R, DB 48 weeks	Low	Women at risk of HIV (Botswana, Kenya, Malawi, South Africa, eSwatini [formerly Swaziland], Uganda and Zimbabwe)	HIV incidence	Not used
TD/FTC versus SoC						
iPrEx	2,499	R, DB, 2.8 years	Low	MSM at high risk (Peru, Ecuador, Brazil, USA, Thailand, South Africa)	HIV incidence	Three scenarios involving iPrEx results, and meta-analysed results were applied to an indirect comparison against CAB-LA and used in the economic evaluation.
PROUD	544	R, OL, 24 months	High	MSM at high risk (England)	HIV incidence	
IPERGAY	414	R, DB 24 months	Low	MSM (France, Canada)	HIV incidence	

Source: pp39–158 of the submission, Appendix 1 to the submission, Tenofovir disoproxil /emtricitabine July 2016 PSD, Truvada July 2017 PSD.

CAB-LA = cabotegravir; long acting; DB = double blind; MC = multi-centre; HIV = human immunodeficiency virus; MSM = men who have sex with men; OL = open label; R = randomised; SoC = standard of care; TD/FTC = tenofovir disoproxil / emtricitabine; TGW = transgender women; USA = United States of America.

- 6.8 The PBAC previously evaluated the iPrEx, PROUD and IPERGAY trials in the context of TD/FTC oral PrEP submissions. Of the trials used in the indirect comparisons, IPERGAY and iPrEx were previously considered by the PBAC to have a low risk of bias, and the PROUD trial was considered to have a high risk of bias (TD/FTC, Public Summary Document (PSD), July 2016 and July 2017 PBAC meetings).
- 6.9 None of the included trials included individuals who were contraindicated to or were intolerant to TD/FTC. Additionally, in the HPTN-083 and HPTN-084 trials, only participants who had at least 50% adherence to the oral tablets were permitted to progress to injections. Consequently, none of the participants enrolled in the included trials reflected the requested population and represents a significant applicability issue.
- 6.10 The PSCR argued the exclusion of participants with contraindications to oral PrEP from the trial program is not expected to impact the applicability of the relative treatment effect from the trials to the Australian clinical setting. Further, the PSCR argued there was no evidence to suggest the treatment effect of CAB-LA would differ in patients intolerant or sub-optimally adherent to oral PrEP where discontinuation of oral PrEP is necessitated, and stated the protocol defined discontinuation during the oral lead-in phase was to minimise the potential for bias in favour of CAB-LA, given the known confounding of adherence on oral PrEP effectiveness.

- 6.11 The ESC acknowledged that the trial design excluded patients who were non-adherent to oral PrEP and considered this did not necessarily limit the generalisability of the HPTN-083 and -084 trials to the proposed population in and of itself (but noted that efficacy in the suboptimal adherence population can only be inferred from the available evidence). However, the ESC considered the locations in which the trials were undertaken was problematic when considering the applicability of the trial to the Australian setting, due to differences in health systems, access to oral PrEP, level of awareness in the population most likely to be using PrEP and underlying differences in HIV infection risk. Overall, the ESC considered these applicability issues meant the observed results would likely overestimate the comparative effectiveness of CAB-LA relative to TD/FTC in the Australian setting.
- 6.12 HPTN-083 was a non-inferiority trial with a non-inferiority margin of 1.23. The statistical analysis plan (SAP) stated that the non-inferiority margin was based on an inverse variance weighted meta-analysis of iPrEx, IPERGAY, and PROUD but did not clearly lay out a statistical plan for demonstrating superiority (though the submission suggested that the superiority margin was 1), and implied that superior results would be due to lower adherence in the TD/FTC group. In describing statistical power, the SAP noted that at a superiority margin of 0.74 (indicating a 26% advantage of CAB-LA over TD/FTC), the power to detect superiority was only 47%. It was unclear whether any alpha spending was required to address the multiplicity testing of both non-inferiority and superiority, as while the type I error for the non-inferiority margin was specified, no alpha for the superiority margin was provided. While the submission did not make a claim of superior efficacy over TD/FTC, the results used in the indirect comparison implied superior efficacy with CAB-LA over TD/FTC.
- 6.13 The PSCR argued the superiority of CAB-LA over TD/FTC has been accepted by regulators (including the TGA), given it was accepted for consideration under priority review and whilst the HPTN-083 trial was designed as a non-inferiority trial, it also allowed for establishing superiority as outlined in the trial protocol and statistical analysis plan. The PSCR provided an attachment on the interpretation of the HPTN-083 results prepared by the Protocol Statisticians and Chair of the HPTN Study Monitoring Committee. The attachment outlined the trial was designed with interim monitoring of the non-inferiority margin of 1.23 at approximately 25%, 50% and 75% for the planned 172 events, using an O'Brien-Fleming boundary. At the first interim analysis (May 2020), an independent data safety monitoring board determined the O'Brien-Fleming boundary had been crossed and recommended the blinded conduct of the trial should be terminated. The PSCR stated the primary analysis in HPTN-083 demonstrated a 66% reduction in the risk of acquiring incident HIV infection (HR 0.34, 95% CI 0.18, 0.62, $p=0.0005$) for CAB-LA relative to TD/FTC in HIV-uninfected cisgender men and transgender women who have sex with men, and argued this not only establishes the efficacy of CAB-LA by reliably ruling out the 1.23 non-inferiority margin ($p<0.0001$), but also provides statistically significant evidence of superiority relative to TD/FTC (ruling out a HR of 1.0 with $p=0.0005$).

- 6.14 The ESC considered the statistical approach used in the HPTN-083 trial to assess a claim of superiority of CAB-LA over TD/FTC may be reasonable (however it was unclear if any alpha spending was required in this situation), but statistical validity did not add additional certainty to the applicability of the studies to the Australian setting.
- 6.15 In the HPTN-083 study, overall adherence in the TD/FTC adherence cohort reported 84% of samples yielded plasma tenofovir (TFV) concentrations of ≥ 4 doses/week. In addition, 77% of samples had TFV concentrations of greater than 35.5 ng/mL which is consistent with the receipt of daily TD/FTC doses. Adherence to TD/FTC in the HPTN-084 study was comparably lower; 44% of evaluated samples yielded plasma TFV concentrations consistent with seven doses per week and 52% of evaluated samples yielded plasma TFV concentrations consistent with ≥ 4 doses per week. The PSCR reiterated the submission supported the applicability of adherence to oral PrEP observed in the HPTN-083 study and presented the reported aggregate estimates for oral PrEP adherence in the Australian setting including the mean overall medication possession ratio (MPR) of TD/FTC of 80.7% among participants in the EPIC-NSW study over 26 months of follow-up⁵; and an MPR of 80.8% based on prescribing data from a DUSC analysis on PrEP utilisation⁶. The PSCR noted the HPTN-083 study observed a similar rate to these analyses, where 84% of samples from the TD/FTC adherence cohort yielded plasma tenofovir concentrations indicative of 4 or more doses per week. The PSCR also noted an economic model from the Kirby Institute, previously used to support TD/FTC applications, assumed an adherence of 90% (tenofovir/emtricitabine PSD, December 2017 PBAC meeting).
- 6.16 The ESC considered measuring adherence in the Australian setting was complicated due to the likely high uptake of on-demand PrEP regimens, which does not constitute suboptimal adherence in some groups, but would constitute non-adherence in the pivotal trials and considered it was difficult to compare adherence between these settings.
- 6.17 While no real-world estimates of adherence to CAB-LA have been presented, it is plausible that adherence to injections would be lower in the real world setting compared to the HPTN-083 trial setting. The extent to which lower adherence to CAB-LA and delayed injection visits could impact effectiveness in the Australian treatment setting was uncertain.
- 6.18 The submission considered PROUD to have high adherence (88%) based on TFV detection in samples from 52 participants. In IPERGAY, in the TD/FTC group, the rates

⁵ Jin F, Amin J, Guy R, Vaccher S, Selvey C, Zablotska I, Holden J, Price K, Yeung B, Ogilvie E, Quichua GC, Clackett S, McNulty A, Smith D, Templeton DJ, Bavinton B, Grulich AE; Expanded PrEP Implementation in Communities New South Wales (EPIC-NSW) research group. Adherence to daily HIV pre-exposure prophylaxis in a large-scale implementation study in New South Wales, Australia. *AIDS*. 2021 Oct 1;35(12):1987-1996.

⁶ DUSC 2021. Pre-exposure prophylaxis: Utilisation analysis using MedicineInsight data – October 2021. DUSC 2021. <https://www.pbs.gov.au/info/industry/listing/participants/public-release-docs/2021-10/nps-analysis-of-medications-for-prep-using-medicineinsight>

of detection were 86% for TFV and 82% for FTC. In the TD/FTC group in iPrEx, at least one of the study drug components was detected in 22 of 43 of seronegative subjects (51%) and in 3 of 34 HIV-infected subjects (9%). However, the rate of pill use according to pill count increased during the first 8 weeks and then remained stable at a median ranging from 89 to 95%. The submission considered iPrEx to have moderate adherence.

- 6.19 Adherence in the Australian setting was informed by DUSC analyses. A DUSC analysis on PrEP utilisation using PBS data between April 2018 and March 2021 found that individuals accessing TD/FTC had an average of 8.0 prescriptions for PrEP over the 3 year study period, or 4.4 prescriptions per person-year, equating to a medication possession ratio (MPR) of 36.7% (DUSC 2021)⁷. However, a DUSC analysis using MedicinesInsight data on prescribing conducted in parallel found that the average number of scripts was 9.7 per person-year (based on the number of prescriptions recorded), equating to an MPR of 80.8% (DUSC 2021). The lower estimate based on PBS data may be explained by individuals taking on-demand/event-driven dosing, which was likely to have become more prominent since the ASHM guidelines were updated in 2020, or individuals periodically cycling on and off PrEP due to changes in risk behaviour, thereby limiting the interpretation of the estimated MPR from this PBS analysis. The evaluation considered that this data did not inform the adherence in the proposed 'second line' population and the adherence in the proposed PBS population was unknown. Overall, it was uncertain whether the adherence of TD/FTC in the included trials was similar to the proposed PBS population which limits the applicability of the data from the trials.

Comparative Effectiveness

- 6.20 In HPTN-083, a total of 52 individuals acquired HIV infection after enrolment with 6,405 person-years of follow-up and were included in the pre-specified primary efficacy analysis. Of the 52 individuals who acquired HIV during the trial, 13 were randomised to CAB-LA (incidence, 0.40 per 100 person-years) and 39 were randomised to the TD/FTC group (incidence, 1.22 per 100 person-years).
- 6.21 The submission claimed that the primary analysis demonstrated the superiority of CAB-LA compared to TD/FTC with a 66% reduction in the risk of acquiring incident HIV infection (hazard ratio [HR] = 0.34; 95% confidence interval [CI]: 0.18, 0.62; p=0.0005). The upper bound of the 95% CI was lower than both the non-inferiority margin of 1.23 and the superiority margin of 1. A summary of the Cox proportional hazards model for time to infection for the HPTN-083 trial is presented in the table below.

⁷ DUSC 2021a. Pre-exposure prophylaxis: Utilisation analysis using PBS data – October 2021. DUSC 2021. <https://www.pbs.gov.au/info/industry/listing/participants/public-release-docs/2021-10/nps-analysis-of-medications-for-prep-using-pbs-data>

Table 5: Summary of the Cox proportional hazards regression model for time-to-infection for Steps 1 and 2 (mITT population) HPTN-083

Treatment arm	CAB-LA	TD/FTC
N	2280	2281
Number of participants infected	13	39
PY	3211	3193
Incidence rate (95% CI), per 100 PY ^a	0.40 (0.22, 0.69)	1.22 (0.87, 1.67)
HR (95% CI)	Cox regression Superiority p-value Non-inferiority p-value	0.328 (0.18, 0.61) ^b p = 0.0005 p < 0.0001
	Bias-adjusted, corrected for early stopping ^c Superiority p-value Non-inferiority p-value	0.340 (0.18, 0.62) p = 0.0005 p < 0.0001

Source: Table 29, p76 of the submission.

CAB-LA = cabotegravir long-acting; CI = confidence interval; HR = hazard ratio; PY = person-years; TD/FTC = tenofovir disoproxil /emtricitabine.

HR < 1.0 indicates a lower risk on CAB-LA as compared to TD/FTC. The p-values are two-sided. The trial was stopped based on a breach of the first interim stopping bound ($z = -4.00$, $p\text{-value} = 0.000063$), which was derived from an O'Brien-Fleming design with three planned interim analysis plus one final analysis.

a The 95% CI for incidence rate is calculated using the exact Poisson method.

b The unadjusted hazard ratio is based on a Cox proportional hazards model stratified by region.

c The bias-adjusted hazard ratio, CI, and p-value account for the group-sequential trial design and the early stopping time. The adjusted point estimate is the Median Unbiased Estimate (MUE), and the confidence interval and p-value are based on the Maximum Likelihood Estimate (MLE) ordering of the sample space.

6.22 The HPTN-083 trial demonstrated non-inferiority of CAB-LA to TD/FTC. Though the results favoured CAB-LA, given the issues with the superiority margin and the importance of trial-based adherence in producing the difference in HIV outcomes, it was unclear whether CAB-LA could be considered superior to TD/FTC at HIV prevention in MSM and TGW who have sex with men based on the HPTN-083 results. The trial did, however, suggest that CAB-LA would be at least as effective as TD/FTC, and possibly be more effective (depending on adherence) in preventing HIV infection in HIV uninfected MSM and TGW who have sex with men.

6.23 In HPTN-084, at the end of Step 2 (blinded study termination), 40 incident HIV-1 infections were reported for the modified intent-to-treat (mITT) population over 3907 person-years of follow-up, giving an overall incidence for the entire study population of 1.02 per 100 person-years. Of the 40 incident HIV-1 infections, four occurred in the CAB-LA group (incidence of 0.20 per 100 person-years) and 36 occurred in the TD/FTC group (incidence of 1.85 per 100 person-years). The bias adjusted (corrected for early stopping) HR of 0.12 (95% CI: 0.05, 0.31) indicates there was an 88% reduction in the incidence of HIV-1 infections during Steps 1 and 2 for participants in the CAB-LA group relative to participants in the TD/FTC group. A summary of the Cox proportional hazards model for the HPTN-084 trial is presented in the table below.

Table 6: Summary of the Cox proportional hazards regression model for time-to-infection for Steps 1 and 2 (mITT Population) HPTN-084

Treatment	CAB-LA	TD/FTC
N	1614	1610
Number of participants infected	4	36
PY	1961	1946
Incidence rate (95% CI), per 100 PY ^a	0.20 (0.06, 0.52)	1.85 (1.30, 2.56)
HR (95% CI) ^b , superiority value	Cox regression	0.11 (0.04, 0.31), p < 0.0001
	Bias-adjusted, corrected for early stopping ^c	0.12 (0.05, 0.31), p < 0.0001

Source: Table 34, p81 of the submission.

CAB-LA = cabotegravir long-acting; CI = confidence interval; HR = hazard ratio; PY = person-years; TD-FTC = tenofovir disoproxil - emtricitabine.

a The 95% CI for incidence rate was calculated using the exact Poisson method.

b Hazard ratio < 1.0 indicates a lower risk on CAB-LA as compared to TD/FTC. The HR is based on a Cox proportional hazards model stratified by site.

c The bias-adjusted HR, CI, and p-value account for the group-sequential trial design and the decision to stop the trial at the second interim analysis. This was calculated outside of this report using additional data from the first interim analysis that is not part of the submission data package used for this report.

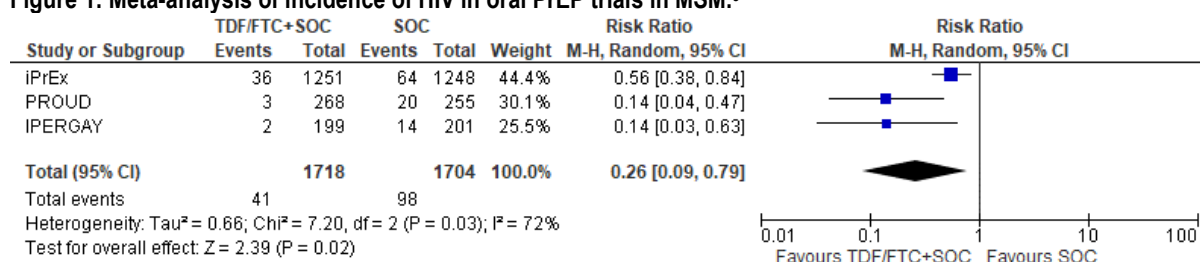
- 6.24 HPTN-084 demonstrated improved protection from HIV infection for CAB-LA relative to TD/FTC in cisgender women in Africa. As with HPTN-083, adherence may have been a key driver of effect.
- 6.25 Another possible reason for improved relative effect of CAB-LA versus TD/FTC in women may be sex-related pharmacokinetics. Some studies suggest that customary dosing regimens of TD may not produce adequate concentrations in the female genital tract for the purposes of protection against acute HIV infection and may help explain variable oral PrEP efficacy by sex (Bailey 2017).⁸
- 6.26 HPTN-084 results were not used in the indirect comparison or the economic evaluation due to the limited applicability of HPTN-084 which included cisgendered women in sub-Saharan Africa. The evaluation considered that this was reasonable.
- 6.27 The submission considered that due to heterogeneity between the HPTN 083 and HPTN 084 trials, primarily in terms of varying populations (MSM and TGW compared to cisgender women) and varying levels of adherence to TD/FTC, combining the results of these trials using meta-analytic methods was not considered appropriate. The evaluation considered that this was reasonable.
- 6.28 The submission argued that, for the TD/FTC versus SoC trials, considerable heterogeneity across the trials of oral PrEP compromised the ability to perform meta-analysis on the overall dataset.
- 6.29 In the consideration of TD/FTC for HIV PrEP, the PBAC previously considered that the ‘meta-analysis provided in the submission is considered to be of limited value due to the highly heterogeneous combination of trials’ (paragraph 6.7, TD/FTC, PSD July 2016 PBAC meeting). Consequently the submission explored alternative approaches to

⁸ Bailey JL, Molino ST, Vegaa AD and Badowsky M. 2017. A review of HIV Pre-Exposure Prophylaxis: The Female perspective. Infectious diseases and therapy. 6 (3): 363-382. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5595773/>

meta-analysing the data on HIV incidence for oral PrEP, including stratifying trial results by enrolled individual populations and levels of adherence.

- 6.30 The submission constructed two meta-analyses of TD/FTC versus SoC to inform different scenarios in the indirect comparisons. Figure 1 presents the meta-analysis of incidence of HIV in oral PrEP trials for the included comparator trials. This meta-analysis of HIV incidence from the three trials of oral PrEP in MSM resulted in an overall HR of 0.26 (95% CI: 0.09, 0.79), indicating a 74% risk reduction in the rate of HIV acquisition ($I^2=72%$) with TD/FTC relative to no PrEP⁹.

Figure 1: Meta-analysis of incidence of HIV in oral PrEP trials in MSM.⁹



Source: Figure 23, p111 of the submission.

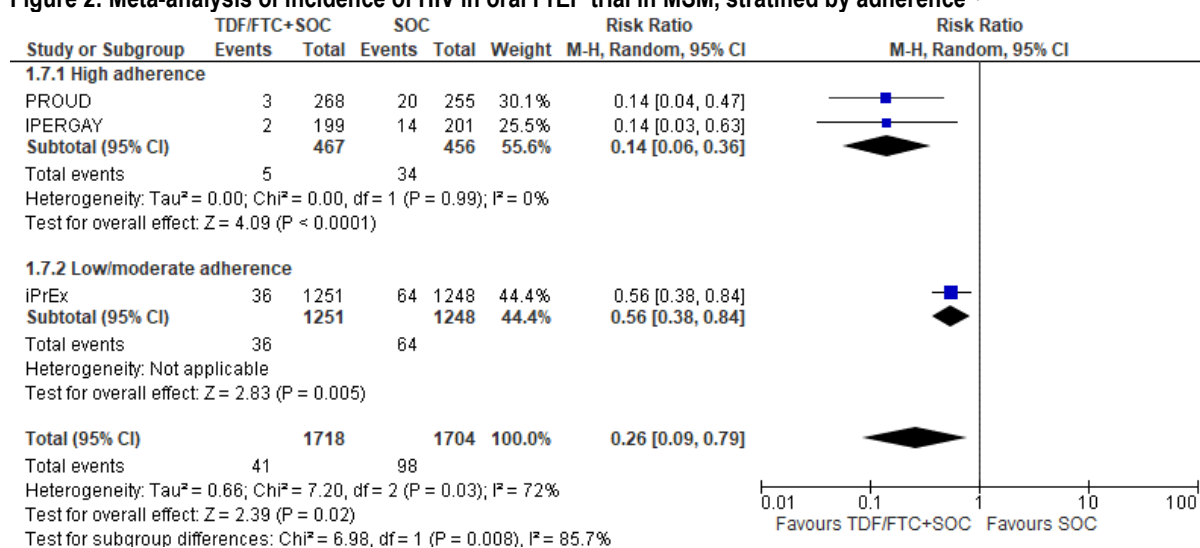
CI = confidence interval; HIV = human immunodeficiency virus; M-H = Mantel-Haenszel; MSM = men who have sex with men; PrEP = pre-exposure prophylaxis; SoC = standard of care; TD/FTC = tenofovir disoproxil and emtricitabine.

Performed using standard random effects meta-analyses using Review Manager software.

- 6.31 The submission proposed that the heterogeneity between trials was largely driven by differences in levels of adherence between the trials, given the established correlation between adherence and efficacy in HIV PrEP. The submission also considered that treatment effect in the iPrEx trial may have been underestimated due to relatively poor levels of adherence to study drug in the study.
- 6.32 In contrast, the submission attributed the higher efficacy in PROUD and IPERGAY to higher adherence. The submission presented a stratified analysis of studies reporting high adherence to study drug and identical efficacy (i.e., PROUD and IPERGAY), statistical heterogeneity was eliminated ($I^2=0%$) and the risk reduction of HIV acquisition was 86% (HR: 0.14, 95% CI: 0.06, 0.36)⁹. These data are presented in Figure 2.

⁹ Note that the results in paragraph 6.30, Figure 1 and 6.32 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

Figure 2: Meta-analysis of incidence of HIV in oral PrEP trial in MSM, stratified by adherence¹⁰



Source: Figure 24, p111 of the submission.

CI = confidence interval; HIV = human immunodeficiency virus; M-H = Mantel-Haenszel; MSM = men who have sex with men; PrEP = pre-exposure prophylaxis; SoC = standard of care; TD/FTC = tenofovir disoproxil and emtricitabine.

Performed using standard random effects meta-analyses using Review Manager software.

- 6.33 The submission considered that despite the moderate heterogeneity, combined results from these three trials may represent an average relative treatment effect that better represents TD/FTC efficacy in a more adherent population, and which more closely aligns with the adherence to TD-FTC observed in HPTN 083. However, this would reduce the transitivity with HPTN-083, which had a similar adherence to PROUD and IPERGAY.
- 6.34 The evaluation considered that none of the included trials formed a reasonable basis for estimating adherence to (and efficacy of) TD/FTC in the proposed population in whom PrEP was indicated but who are not taking TD/FTC (due to contraindication, intolerance, or sub-optimal adherence).
- 6.35 Of the scenarios presented above, including iPrEx only (low adherence) leads to the most conservative indirect comparison result with a higher HR when comparing CAB-LA to SoC.
- 6.36 The submission presented three scenarios according to the trials of TD/FTC vs. SoC:
- Scenario 1: the indirect comparison of CAB-LA vs. SoC, using the iPrEx trial alone, results in an indirect estimate HR of 0.19 (95% CI: 0.09, 0.401; p<0.001)¹⁰, indicating an 81% reduction in the risk of HIV acquisition with CAB-LA relative to no biomedical PrEP. While the exchangeability of iPrEx and HPTN 083 is supported

¹⁰ Note that the results in Figure 2 and paragraph 6.36 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

in terms of population, study location and methodology, the key difference with respect to levels of adherence in the common TD/FTC arm, biases the results of this indirect comparison against CAB-LA. In addition to adherence, the SoC arm had the lowest event rate, suggesting that baseline risk in iPrEx was lower than in the open label PROUD trial and the IPERGAY trial. This was numerically the most conservative scenario presented by the submission but as the HIV infection rate in the SoC arm of iPrEx remains substantially higher than the Australian population, there remains applicability issues with this estimate.

- Scenario 2: the indirect comparison based on the meta-analysed result of all three trials of oral PrEP in MSM (HR: 0.26; 95% CI: 0.09, 0.79)¹¹, the indirect risk estimate for CAB-LA vs. SoC is 0.088 (95% CI: 0.025, 0.308)¹¹; $p < 0.001$, indicating a 91.2% reduction in the risk of HIV acquisition with CAB-LA relative to no biomedical PrEP. This analysis was used as the base case in the economic evaluation.
- Scenario 3: trials of TD/FTC vs. SoC in the setting of high adherence more closely resembling levels of adherence (PROUD and IPERGAY) in the common reference arm of HPTN 083, result in an indirect risk estimate of 0.048 (95%CI: 0.016, 0.141)¹¹; $p < 0.001$, indicating a 95.2% reduction in the risk of HIV acquisition.

6.37 A summary of the results of the Bucher indirect treatment comparison of CAB-LA vs. SoC, via TD/FTC as the common reference, for the incidence of HIV is presented in Table 7.

¹¹ Note that the results in paragraph 6.36 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

Table 7: Indirect treatment comparison of CAB-LA vs. SoC for HIV incidence in MSM¹²

Study	n/N (%)	HIV per 100 PY	n/N (%)	HIV per 100 PY	n/N (%)	HIV per 100 PY	Risk estimate [HR] (95% CI) ^a	RRR (95% CI) ^a	p-value
	CAB-LA + SoC		TD/FTC + SoC		SoC		CAB-LA vs. TD/FTC		
HPTN 083	13/2280 (0.6%)	0.40	39/2281 (1.7%)	1.22	-	-	0.34 (0.18,0.62)	0.66 (0.38,0.82)	< 0.001
	CAB-LA + SoC		TD/FTC + SoC		SoC		TD/FTC +SoC vs. SoC		
iPrEx	-	-	36/1251 (2.9%)	2.2 ^b	64/1248 (5.1%)	3.9 ^b	0.56 (0.37,0.85)	0.44 (0.15,0.63)	0.005
PROUD	-	-	3/268 (1.1%)	1.2	20/255 (7.8%)	9.0	0.14 (0.04,0.36) ^c	0.86 (0.64,0.96) ^c	0.0001
IPERGAY	-	-	2/199 (1.0%)	0.91	14/201 (7.0%)	6.60	0.14 (0.02,0.60)	0.86 (0.40,0.98)	0.002
	Trials of TD/FTC vs. SoC		CAB-LA vs TD/FTC (HPTN 083) Risk estimate; HR (95%CI)		TD/FTC vs SoC Risk estimate; HR (95%CI)		CAB-LA vs. SoC, via TD/FTC Indirect risk estimate; HR (95%CI)^d		
Scenario 1	iPrEx		0.340 (0.18, 0.62)		0.56 (0.37, 0.85)		0.19 [0.09, 0.401]; p<0.001		
Scenario 2	iPrEx, PROUD, IPERGAY		0.340 (0.18, 0.62)		0.26 (0.09, 0.79)		0.088 [0.025, 0.308]; p<0.001		
Scenario 3	PROUD, IPERGAY		0.340 (0.18, 0.62)		0.14 (0.06, 0.36)		0.048 [0.016, 0.141]; p<0.001		

Source: Table 44, p110 and Table 45, p112 of the submission.

CAB-LA = cabotegravir long-acting; CI = confidence interval; HR = hazard ratio; PY = person-years; RRR = relative risk reduction; SoC = standard of care; TD/FTC = tenofovir disoproxil and emtricitabine.

a Where not reported, risk/hazard ratios were calculated as the inverse of reported relative risk reduction (and vice versa).

b Publication does not report incidence rate per 100 person-years. These values are calculated assuming equivalent person-years of follow-up in both treatment arms (i.e. 3324/2).

c Publication reports 90% confidence interval for the relative risk reduction; HR calculated based on this 90% CI

d Performed using the Bucher ITC method (See "CABvsSoC_BucherITC".xls in Attachment 4 for calculations). Nb. Inverse of result for TD/FTC vs. SoC applied in the ITC.

Grey shaded scenario indicates scenario used in base case of economic evaluation

6.38 The baseline HIV risk (in terms of HIV incidence) in the countries where the HPTN-083 trials were conducted was likely substantially different to PROUD and IPERGAY (refer to Table 4), which poses a potential exchangeability issue. HPTN-083 was conducted in countries with a relatively high incidence of HIV whereas IPERGAY and PROUD were conducted in countries with a lower incidence.

6.39 Further, the HIV incidence rate in men in Australia in 2020 was approximately 4.5 per 100,000¹³, which was 31-58% lower than 'similar' countries (i.e. France and UK) as proposed by the submission and may represent an applicability issue, and it was

¹² Note that the results in Table 7 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

¹³ Kirby Institute (2021), 'HIV, viral hepatitis and sexually transmissible infections in Australia Annual surveillance report 2021' https://kirby.unsw.edu.au/sites/default/files/kirby/report/Annual-Surveillance-Report-2021_HIV_221107.pdf

uncertain as to whether the estimated incremental effect in the indirect comparison would be realised in the proposed PBS population.

- 6.40 Similarly, the baseline HIV risk in the PROUD, IPERGAY and iPrEx trials also indicated large differences in baseline HIV risk to the Australian setting based on HIV infection rates in the SoC arm (e.g. a baseline rate of 1.4 per 100 person years was applied in the economic evaluation in the SoC population, compared to 3.9-9.0 in the TD/FTC versus SoC trials). This further suggested that the indirect comparison had overall poor applicability to the Australian population. The PSCR noted that reported incidence rates vary within populations due to diversity among at-risk populations. On that basis, the PSCR argued that even in the Australian context, where the overall general population-level HIV incidence is relatively low, the potential for the risk of HIV acquisition at an individual level to be higher should not be discounted.
- 6.41 The PSCR argued that since the effectiveness of TD/FTC had been shown to strongly correlate with adherence, the treatment effect for oral PrEP in the iPrEx trial was likely underestimated. The PSCR argued that as a result the relative risk reduction of HIV acquisition for CAB-LA vs SoC of 81% using the iPrEx trial alone likely biases against CAB-LA. The PSCR stated that in order to provide a transparent method of adjusting for the relative treatment effect of CAB-LA vs SoC, the PROUD and IPERGAY trials, which reported adherence rates more closely aligned with the HPTN-083 trial, were included in the direct estimate of effect for TD/FTC vs SoC along with the iPrEx trial, resulting in a relative risk reduction of 91.2% for CAB-LA relative to SoC. The PSCR also noted other independently published estimates of the effectiveness of CAB-LA vs SoC were supportive of the effectiveness result from the ITC presented in the submission, including Mitchell 2023¹⁴, which estimated CAB-LA PrEP effectiveness in the MSM population to be 91% (82-96%), with other epidemiological mathematical modelling studies using estimates of CAB-LA effectiveness of a comparable magnitude, such as Smith 2023¹⁵ and Jamieson 2022¹⁶.
- 6.42 The PSCR stated that the submission applied the results of the relative treatment effects from the included trials of CAB-LA and TDF/FTC to derive an indirect estimate of effect for CAB-LA vs. SoC, which is then applied to a background incidence of HIV reported in a DUSC analysis. The PSCR argued that the integration of relative effect measures together with local HIV incidence (1.4 cases per 100 person-years in Australian MSM) within the economic model allows for the estimation of the absolute

¹⁴ Mitchell, K. M., et al. (2023). "Estimating the impact of HIV PrEP regimens containing long-acting injectable cabotegravir or daily oral tenofovir disoproxil fumarate/emtricitabine among men who have sex with men in the United States: a mathematical modelling study for HPTN 083." *The Lancet Regional Health – Americas* 18.

¹⁵ Smith J et al (2023). Predicted effects of the introduction of long-acting injectable cabotegravir pre-exposure prophylaxis in sub-Saharan Africa: a modelling study. *Lancet HIV*. 2023 Apr;10(4):e254-e265.

¹⁶ Jamieson, L., et al. (2022). "Relative cost-effectiveness of long-acting injectable cabotegravir versus oral pre-exposure prophylaxis in South Africa based on the HPTN 083 and HPTN 084 trials: a modelled economic evaluation and threshold analysis." *The Lancet HIV* 9(12): e857-e867.

magnitude of impact (in terms of infections averted) that would be expected in the local population.

- 6.43 The ESC considered, given the applicability issues to the Australian setting identified (paragraph 6.11) and uncertainties arising from the impact of adherence of oral PrEP to the observed results of both the pivotal trials and the reference TD/FTC vs SoC trials, that the estimates of CAB-LA presented in the submission were likely to be overstated in the Australian setting, both versus TD/FTC and SoC.

Comparative Harms

- 6.44 Table 8 presents a summary of all treatment emergent (TE) adverse events (AEs) in the HPTN-083 and HPTN-084 trials.

Table 8: Summary of all TEAEs in HPTN 083 and HPTN -084 (Safety Population; Steps 1 and 2)¹⁷

AEs	CAB-LA (N=2281)	TD/FTC (N=2285)	RR (95% CI)	RD (95% CI)
	n/N (%)	n/N (%)	< 1 favours CAB-LA	< 0 favours CAB-LA
HPNT-083				
Any AE	2174/2281 (95.31)	2157/2285 (94.40)	1.01 (1.00, 1.02)	0.01 (0.00, 0.02)
Drug-related	1874/2281 (82.16%)	1355/2285 (59.30%)	1.39 (1.33, 1.44)	0.23 (0.20, 0.25)
ISR AEs	1740/2281 (76.28%)	726/2285 (31.77%)	2.40 (2.25, 2.56)	0.45 (0.42, 0.47)
Drug-related ISR AEs	1724/2281 (75.58%)	652/2285 (28.53%)	2.65 (2.47, 2.84)	0.47 (0.44, 0.50)
Injection site pain	1713/2281 (75.10%)	688/2285 (30.11%)	2.49 (2.33, 2.67)	0.45 (0.42, 0.48)
Blood glucose increased	247/2281 (10.83%)	166/2285 (7.26%)	1.49 (1.24, 1.80)	0.04 (0.02, 0.05)
Pyrexia	232/2281 (10.17%)	112/2285 (4.90%)	2.08 (1.67, 2.58)	0.05 (0.04, 0.07)
Injection site swelling	206/2281 (9.03%)	9/2285 (0.39%)	22.93 (11.79, 44.58)	0.09 (0.07, 0.10)
HPTN-084				
Any AE	1556/1614 (96.41%)	1540/1610 (95.65%)	1.01 (0.99, 1.02)	0.01 (-0.01, 0.02)
Drug-related	1098/1614 (68.03%)	1014/1610 (62.98%)	1.08 (1.03, 1.14)	0.05 (0.02, 0.08)
Drug-related ISR AE	575/1614 (35.63%)	163/1610 (10.12%)	3.52 (3.00, 4.13)	0.26 (0.23, 0.28)
Injection site pain	522/1614 (32.34%)	147/1610 (9.13%)	3.54 (2.99, 4.20)	0.23 (0.20, 0.26)
Injection site nodule	80/1614 (4.96%)	5/1610 (0.31%)	15.96 (6.48, 39.29)	0.05 (0.04, 0.06)
Blood glucose increased	584/1614 (36.18%)	451/1610 (28.01%)	1.29 (1.17, 1.43)	0.08 (0.05, 0.11)
Injection site swelling	105/1614 (6.51%)	5/1610 (0.31%)	20.95 (8.56, 51.24)	0.06 (0.05, 0.07)

Source: Table 37, p87, Table 38, p90, Table 40, p96 and Table 41, pp99-100 of the submission

AE = adverse event; CAB-LA = cabotegravir long-acting; CI = confidence interval; ISR = injection site reaction; NE = not estimable; RD = risk difference; RR = risk ratio; SAE = serious adverse event; TD/FTC = tenofovir disoproxil /emtricitabine.

- 6.45 The safety results of HPTN-083 and HPTN-084 indicated more frequent injection site related AEs in individuals treated with CAB-LA compared to individuals treated with TD/FTC (even though individuals treated with TD/FTC also received a sham injection).
- 6.46 The submission presented a comparative assessment of safety outcomes based on the HPTN-083 trial and available data reported for the studies of TD/FTC versus SoC in MSM. HPTN-084 was not included in the comparison as the trial did not include a

¹⁷ Note that the results in Table 8 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

population of MSM. The submission noted that AEs were scarcely reported in the source publication for the PROUD study and are therefore not presented. As the IPERGAY trial was based on on-demand dosing of TD/FTC, which may not be reflective of AEs from daily use, safety data from Partners PrEP and TDF2 (conducted in heterosexual sero-discordant couples and heterosexual men or women, respectively) was also extracted. The VOICE and FEM-PrEP trials were not considered for this safety assessment, given the relatively low adherence (24-29%) to TD/FTC in these studies.

- 6.47 The submission stated that due to inconsistencies in assessment and reporting of AEs across trials, differences in event rates across the common TD/FTC arm, differences in durations of follow-up between the trials, and heterogeneity in safety events reported across trials of TD/FTC vs. SoC to enable pooling, a formal statistical indirect treatment comparison (ITC) for CAB-LA vs. SoC based on safety events was not further explored. The evaluation considered that this was reasonable.
- 6.48 The submission recalled that the PBAC has previously considered that long-term concerns with TD/FTC included impact on bone loss and renal function (paragraph 7.10, TD/FTC, PSD, July 2017 PBAC meeting). The data indicated a trend towards a significantly greater frequency of creatinine elevations with TD/FTC, which was not observed in HPTN-083. The submission noted that although there were no significant differences in the rate of fractures in the TD/FTC versus SoC trials (where reported), which are used as an indicator of adverse bone effects, trial follow-up periods may have been inadequate to fully assess these long-term effects.
- 6.49 Overall, given the heterogeneity across the trials, the comparative assessment did not give a clear assessment of adverse events versus SoC. Nevertheless, given that the PBAC considered the claim of non-inferior comparative safety of TD/FTC compared to SoC was not strongly supported by the available data though the claim was probably reasonable (paragraph 7.10, TD/FTC, PSD, July 2017 PBAC meeting), and that CAB-LA + rilpivirine LA was also non-inferior in safety to oral ART (paragraph 7.8, CAB-LA + rilpivirine LA, PSD, November 2021 PBAC meeting) the clinical claim that CAB-LA has an acceptable and manageable safety profile compared to SoC is likely reasonable, even though injection site reactions (ISRs) were likely to be more common with CAB-LA (which was also the case with CAB-LA + rilpivirine LA). However, there may be longer term safety issues with CAB-LA which are unknown at this point given it is a relatively new treatment.

Benefits/Harms

- 6.50 A summary of the comparative benefits and harms for CAB-LA versus SoC as PrEP in individuals who are able to use TD/FTC is presented in Table 9. There was insufficient information available on the use of CAB-LA as PrEP to determine its benefits and harms versus SoC in the prevention of HIV infection in individuals who were contraindicated or having discontinued TD/FTC due to poor adherence or tolerability. This is because none of the included trials studied the efficacy and safety of CAB-LA in the requested population.

Table 9: Summary of comparative benefits CAB-LA versus SoC

	CAB-LA vs. TD/FTC (HPTN 083) Risk estimate; HR (95% CI)	TD/FTC vs. SoC Risk estimate; HR (95% CI)	CAB-LA vs. SoC, via TD/FTC Indirect risk estimate; HR (95% CI)
HR for HIV incidence rate per 100 person years	0.340 (0.18, 0.62)	0.26 (0.09, 0.79)*	0.088 (0.025, 0.308); p<0.001*
	CAB-LA (HPTN-083)	TD/FTC (HPTN-083)	SoC (indirect comparison)
Incident rate	0.4 cases per 100 person years	1.22 case per 100 person years	4.55 cases per 100 person years ^{a,b}
Economic evaluation incident rates	0.12 cases per 100 person year ^{c,b}	NR	1.4 cases per 100 person years ^d

Source: Table 45, p112 of the submission.

CAB-LA = cabotegravir long-acting; CI = confidence interval; HR = hazard ratio; NR = not reported; SoC = standard of care; TD/FTC = tenofovir disoproxil and emtricitabine.

^a Calculated during the evaluation as $0.4/0.088 = 4.55$.

^b Calculated during evaluation

^c Based on 1.4 cases per 100 person years in SoC, the incidence of HIV for persons treated with CAB-LA was 0.1232 (1.4×0.088).

^d Based on DUSC report of NPS analysis of medications for PrEP using PBS data, October 2021.

* Note that the results denoted by (*) are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.51 Based on the HPTN 083 trial, it was estimated that there was an approximate 66% reduction in the incidence of HIV with CAB-LA versus TD/FTC. Based on a meta-analysis of iPrEx, Proud and IPERGAY it was estimated that there was an approximate 74% reduction in the incidence of HIV with TD/FTC vs SoC. Thus it was estimated that there was an approximate 91% ($1-0.34 \times 0.26$) reduction in the incidence of HIV with CAB-LA versus SoC. The incidence of HIV in the CAB-LA arm of HPTN 083 was 0.40 cases per 100 person years and therefore the incidence with SoC would be 4.55 cases per 100 person years ($0.4 \div 0.088 = 4.55$). In the economic evaluation, the incidence of HIV with SOC was assumed to be 1.4 cases per 100 person years and the incidence of HIV for individuals treated with CAB-LA was 0.1232 per 100 person years (1.4×0.088).

Clinical Claim

6.52 The submission stated that in individuals at risk of HIV infection, CAB-LA as HIV PrEP reduces the risk of HIV infection and has an acceptable and manageable safety profile compared to SoC. Specifically, in individuals at risk of HIV infection and unable to be treated with TD/FTC i.e. as second line treatment.

6.53 Given the substantial applicability issues with the trials stemming from the submission's requested population (which was inconsistent with the population enrolled in the included clinical trials) and nominated comparator, it may be informative to assess alternative clinical claims before assessing the submission's clinical claim.

- On the basis of the HPTN-083 and HPTN-084 trials, it may be reasonable to claim that CAB-LA is at least as effective as TD/FTC in individuals at risk of HIV (however the trial population was in the first-line setting i.e. all individuals who were not

suitable for TD/FTC were excluded from the trials and participants who had less than 50% adherence to the oral lead-in treatment were discontinued); and

- As TD/FTC has been accepted as being superior to SoC, it is logical to accept the claim that CAB-LA is also superior to SoC in this population.

6.54 However, no trial evidence has been included to support a clinical claim in the submission's requested second line population though it may also be reasonable, on balance, to accept a claim of superiority in the second line population. Furthermore, key attributes of the requested population with which to gauge the applicability of the presented evidence remains unknown: specifically, how baseline HIV risk, adherence and any number of other factors in the second line setting differ from the overall PrEP setting.

6.55 While the conclusion of superior efficacy was likely reasonable, the submission's estimates of the magnitude of benefit based on an indirect comparison of CAB-LA to SoC using TD/FTC as the common comparator was highly uncertain and possibly overestimated due to a range of applicability and transitivity issues of the trial data used in the indirect comparison. Specifically,

- None of the trials reflected the 'second line' population. HPTN-083, HPTN-084, PROUD, IPERGAY and iPrEx all reflected a broader population rather than the second-line setting as requested. HPTN-083 and HPTN-084 specifically excluded individuals for whom listing is requested on the basis of contraindication to oral PrEP (individuals under 18 and individuals with CrCL < 60mL/min). The trials also discontinued individuals who had less than 50% adherence to the oral lead-in treatment. These individuals would be more reflective of the population for which listing was sought (i.e. individuals with sub-optimal adherence);
- Adherence differed between the TD/FTC versus SoC trials (PROUD, IPERGAY, iPrEx) and the HPTN-083 trial. The submission attempted to address this through alternative meta-analysed scenarios, but it was unclear whether this was sufficiently addressed;
- The baseline HIV risk in the countries where the HPTN-083 trial was conducted was likely substantially different to PROUD, IPERGAY and iPrEx (which poses a potential exchangeability issue) and to the Australian setting (which poses an applicability issue). Similarly, the baseline HIV risk in the PROUD, IPERGAY and iPrEx trials also indicated large differences in baseline HIV risk to the Australian setting based on HIV infection rates in the SoC arm. Combined, this suggested that the ITC had overall poor applicability to the Australian population and the results may not be realised in the proposed PBS population; and
- It appeared that the estimates of superior effectiveness of CAB-LA relative to TD/FTC in HPTN-083 (and HPTN-084) were primarily driven by sub-optimal adherence in the oral TD/FTC arms.

- 6.56 The ESC considered that a claim of superior comparative effectiveness of CAB-LA to SoC was adequately supported, as the evidence supports a conclusion that CAB-LA is, at minimum, of non-inferior comparative effectiveness to TD/FTC (and TD/FTC is superior to SoC). However, the ESC considered, given the issues outlined above, that a claim of superior comparative effectiveness over TD/FTC was uncertain in the Australian context, and likely to be driven by adherence to oral PrEP in the clinical trials. Therefore, the ESC considered that the magnitude of benefit of CAB-LA over TD/FTC was likely to be overestimated when considering PrEP in the Australian setting.
- 6.57 The Pre-PBAC Response argued the primary analysis in the HPTN-083 trial demonstrated a considerable treatment benefit for CAB-LA relative to an active comparator (TD/FTC), with a 66% reduction in the risk of acquiring HIV infection and stated that while this benefit may have been largely driven by inadequate adherence to TD/FTC among some participants, the challenges of adhering to an effective regimen among certain groups is widely documented. Further, the Response argued that overall adherence to oral TD/FTC was higher than anticipated in the HPTN-083 trial, with 77% of samples measuring plasma tenofovir consistent with 7 doses per week, emphasising the significance of the favourable treatment effect of CAB vs TD/FTC. In addition, the Response argued aggregate adherence to TD/FTC in the Australian setting of approximately 80% (based on real world sources including PBS data) is similar to that observed in the HPTN-083 trial, and therefore the relative treatment effect of CAB vs TD/FTC (HR = 0.34) was appropriate in the Australian context. With regards to the claimed magnitude of benefit over SoC, the Response also argued the effect estimate for TD/FTC vs SoC was derived from a meta-analysis of oral PrEP trials in the MSM population, with varying levels of observed adherence, however the available information for the meta-analysis allows for a transparent method of adjusting the overall effectiveness of PrEP (vs SoC) inputs, given the known confounding of adherence (also discussed in paragraphs 6.42-6.43).
- 6.58 In terms of safety, the submission noted that that the PBAC has previously considered that a claim of superior effectiveness and non-inferior safety for TD/FTC plus SoC relative to SoC was reasonable. This is despite noting that there was an increase in AEs over SoC in trials of TD/FTC, including gastrointestinal events and increased serum creatinine levels as well as the potential that long-term use of TD/FTC may be associated with bone loss and reduced renal function. Overall, the evaluation and ESC considered the submission's claim of an acceptable and manageable safety profile compared to SoC was likely to be reasonable.
- 6.59 The PBAC considered that the claim of superior comparative effectiveness to SoC was reasonable, however considered the claim of superiority over TD/FTC was difficult to assess due to differences between the trial and the Australian setting, including how oral PrEP is used in practice. Overall, the Committee considered a claim that CAB-LA is, at minimum, as effective as TD/FTC was reasonable, however considered it was difficult to draw conclusions about the magnitude of any potential incremental benefit with the available information.

- 6.60 The PBAC considered that the claim of an acceptable and manageable safety profile compared to SoC was reasonable.

Economic Analysis

- 6.61 The submission presented a cost-utility analysis. The economic model was structured as a HIV prevention model, whereby the target PBS population enter the analysis HIV negative, and the incidence of HIV is modelled over a lifetime horizon in individuals receiving CAB-LA compared to SoC. The ESC considered there was substantial uncertainty regarding the magnitude of benefit of CAB-LA over both TD/FTC and SoC in the Australian setting and that was a key driver of uncertainty in the economic analysis.
- 6.62 The indirect comparison of HPTN-083 with iPrEx, PROUD and IPERGAY informed the treatment efficacy of CAB-LA against the primary comparator of SoC via a common comparator of TD/FTC.
- 6.63 Upon contracting HIV, the long-term burden of HIV, in the form of treatment costs and quality adjusted life years (QALYs) were modelled by incorporating the Lim (2022) study, tracing CD4 count overtime and transitioning individuals through three lines of ART.
- 6.64 Individuals could discontinue treatment with CAB-LA based on TD/FTC discontinuation rates (26% at 6-months, then 11.7% every 6 months thereafter) reported in Medland (2023) and transition to SoC with associated costs and risks.

Table 10: Key components of the economic evaluation

Component	Summary
Treatments	CAB-LA versus SoC
Time horizon	Life-time (63 years) time horizon in the model base case versus a maximum of 153 weeks of blinded study in the HPTN-083 trial.
Starting age	37, based on DUSC estimates (DUSC 2021)
Outcomes	HIV cases, Life-years and QALYs
Methods used to generate results	Markov cohort model
Health states	HIV negative health states: CAB-LA at risk of HIV, Post-CAB LA at risk of HIV, SoC at risk of HIV, SoC not at risk of HIV (used only in sensitivity analysis to account for individuals who may still be HIV negative but are no longer at risk of contracting HIV), SoC HIV negative and untreated. HIV positive health states: 4 health states based on CD4 cell count for each of three lines of ART. Dead.
Cycle length	6 months (half cycle corrected)
Transition probabilities or Allocation to health states (if partitioned survival model)	Background HIV risk based on DUSC (2021): 1.4 cases per 100 person years, efficacy based on indirect comparison (RR = 0.088), CAB-LA discontinuation probability based on Medland (2023): 0.117 in first cycle; 0.26 in 2nd and subsequent cycles, CD4 cell count health state and ART line transitions based on Lim (2022). Background all-cause mortality in the economic model was based on Australian life-table values. For HIV health states, an adjustment to mortality risk was made as a function of current CD4 count category based on estimates used in Lim (2022).
Health related quality of life	HIV-negative = 1.00 based on Kirby model assumption HIV: CD4 > 500 (1 st line ART) = 0.935 HIV: CD4 351-500 (1 st line ART) = 0.935 HIV: CD4 201-350 (1 st line ART) = 0.818 HIV: CD4 50-200 (1 st line ART) = 0.702 HIV: CD4 < 50 (1 st line ART) = 0.702 All HIV positive utilities were based on Tengs and Lin (2002).

Source: Table 53, p 133 of the submission.

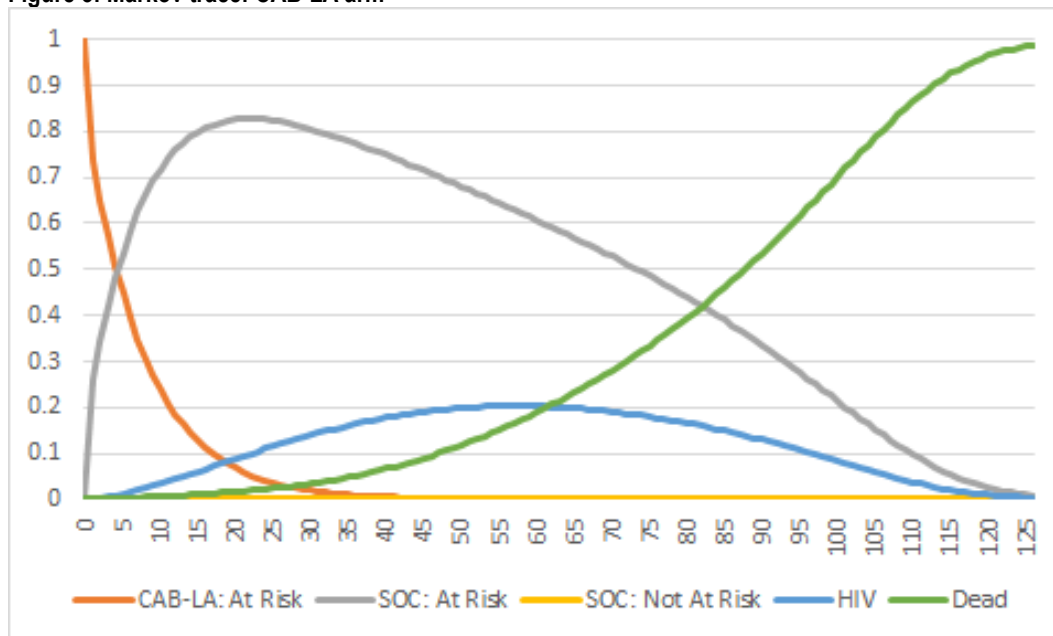
ART = antiretroviral therapy; CAB-LA = cabotegravir long acting; HIV = human immunodeficiency virus; QALY = Quality-adjusted life-year; RR = risk ratio; SoC = standard of care

6.65 The model was most sensitive to changes in time horizon. The PBAC previously considered that a 14-year time horizon provided more certainty (paragraph 7.15, TD/FTC, PSD, July 2017 PBAC meeting). Changing the time horizon from 63 years in the base case to 14 years increased the incremental cost effectiveness ratio (ICER) by 754% to \$155,000 to < \$255,000/QALY. The PSCR argued lifelong costs, morbidity and excess mortality of HIV cases prevented requires a longer time horizon. The PSCR stated that only a lifetime horizon can adequately capture the entirety of these consequences and thus allow a true representation of the cost-effectiveness of CAB-LA, and argued the approach was consistent with the PBAC Guidelines, which state a lifetime horizon is recommended where there is evidence a treatment affects mortality or long-term/ongoing quality of life. The ESC acknowledged there are costs and impacts of HIV infection which affect individuals over a lifetime, but also considered the incidence of HIV infection, and the number of HIV cases to accrue (or avoid) these costs and impacts becomes significantly more uncertain over a longer time horizon, noting the PBAC's previous preference for a shorter time horizon to account for this uncertainty.

- 6.66 The Pre-PBAC Response acknowledged the prevention of HIV cases over a lifetime can become uncertain over such a model duration, however argued the model does not assume the number of HIV cases prevented with CAB-LA increases with time, as 90% of the population have discontinued CAB-LA within 10 years and therefore the impact of model duration on the ICER is driven by lifetime costs and burden of HIV cases avoided in the short term, rather to an uncertain accumulation of HIV cases prevented over a lifetime.
- 6.67 The background rate of HIV infection for the economic evaluation was informed by a 2021 DUSC review of PBS utilisation of HIV and PrEP medications. The report described the incidence of HIV diagnoses by the pattern of PrEP usage. A total of 1.4 (95% CI: 1.0 to 1.8) HIV cases were reported per 100 person-years among discontinued PrEP individuals at least 31 days after commencing PrEP. The DUSC report classified these estimates as a sensitivity analysis and considered that the findings should be interpreted with caution. Specifically, in the sensitivity analysis it was assumed that individuals who started an antiretroviral medicine for HIV up to 30 days after starting tenofovir disoproxil + emtricitabine, were using tenofovir disoproxil + emtricitabine for HIV all along, rather than PrEP, and these individuals were excluded. However, the DUSC report emphasised that a person with HIV may have been misclassified as using TD/FTC for PrEP and that the reliance on a proxy measure of antiretroviral prescriptions for HIV diagnosis may have led to misclassification, for example if some people started on tenofovir alafenamide + emtricitabine (Descovy) for PrEP.
- 6.68 The PSCR acknowledged that the estimate of 1.4 cases per 100 person-years of treatment was intended as a sensitivity analysis only; however argued that given the primary analysis estimated a rate of 3.5 HIV cases per 100 person-years (among discontinued PrEP individuals at least 8 days after commencing PrEP), the former value should be considered conservative and was chosen to reduce uncertainty. The PSCR argued that the DUSC-derived estimate for the risk of HIV infection in the economic model represents the best available data source as it is an Australian dataset, reported in an applicable population for the proposed listing and is objective in nature. The ESC agreed the DUSC estimate was likely the best available estimate of the background rate of HIV infection in the requested population, however noted this estimate remained highly uncertain.
- 6.69 The model was sensitive to changes in the baseline HIV rates (in the SoC arm). Using the lower bound of the DUSC estimate (1.0) increased the ICER by 89% to \$35,000 to < \$45,000/QALY, and using the upper bound (1.8) reduced the ICER by 48.6% to \$5,000 to < \$15,000/QALY.
- 6.70 Altering background risk did not affect the magnitude of relative risk reduction, which could also be lower in a lower risk setting. This represented another source of uncertainty and possibly favours CAB-LA.

- 6.71 The model assumed a constant risk for HIV over time. This was likely unreasonable as HIV notifications appear to vary by age¹⁸, though it was unclear if the same pattern of infection would apply to patients who discontinued PrEP. The submission included sensitivity analyses where HIV negative individuals were assumed to no longer be at risk of HIV contraction after a certain amount of time. These sensitivity analyses indicated that duration of risk was not a key driver of the model. This was likely due to the fact that relative to the lifetime horizon of the model, individuals were only assumed to remain on CAB-LA treatment for a short amount of time, and after discontinuing from CAB-LA, risk of infection was the same in each arm.
- 6.72 Figure 3 presents a Markov trace of transitions in the CAB-LA arm. Most individuals will have discontinued CAB-LA before 5 years (10 cycles), 90% will have discontinued CAB-LA before 9 years (18 cycles).

Figure 3: Markov trace: CAB-LA arm



Source: Figure 39, p170 of the submission.

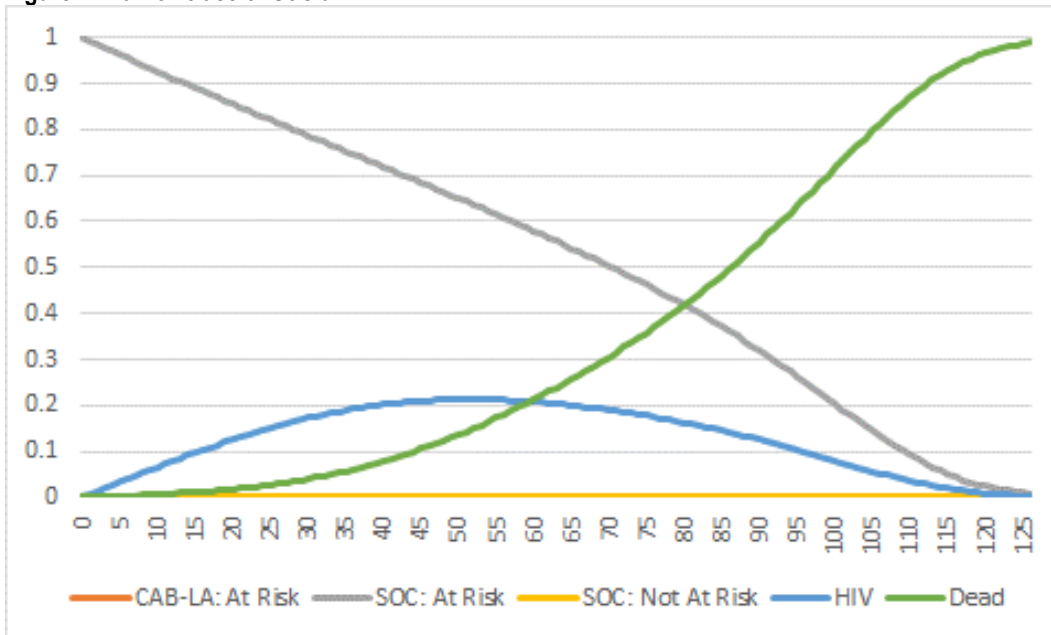
CAB-LA = cabotegravir long acting; HIV = human immunodeficiency virus; SoC = standard of care

Note: the x axis refers to six month cycles.

- 6.73 Figure 4 presents a Markov trace of transitions in the SoC arm.

¹⁸ Kirby Institute (2022), 'HIV, viral hepatitis and sexually transmissible infections in Australia Annual surveillance report 2022; https://kirby.unsw.edu.au/sites/default/files/kirby/report/Annual-Surveillance-Report-2022_HIV.pdf

Figure 4: Markov trace of SoC arm



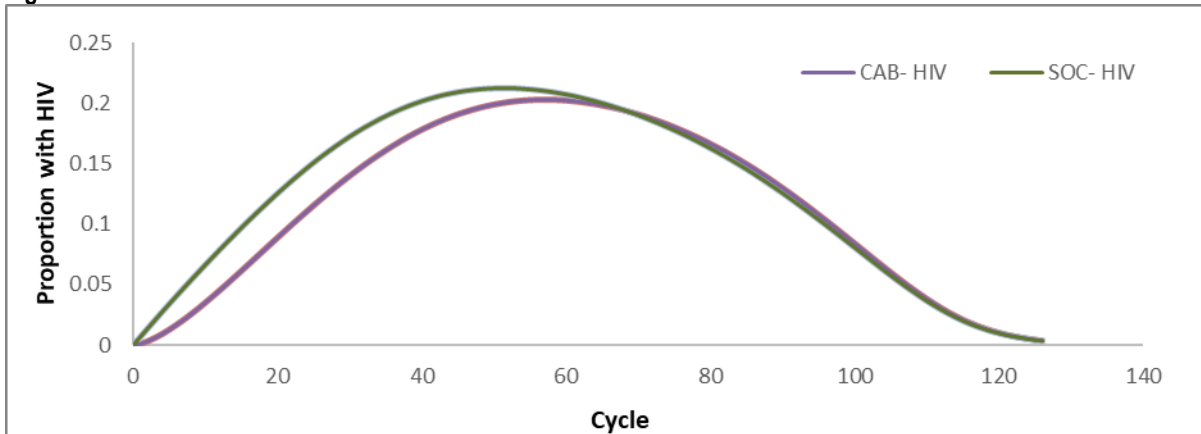
Source: Figure 40, p171 of the submission.

CAB-LA = cabotegravir long acting; HIV = human immunodeficiency virus; SoC = standard of care

Note: the x axis refers to six month cycles.

6.74 A comparison of the proportion of people with HIV by arm in the model is presented in Figure 5.

Figure 5: Markov trace of individuals with HIV in the CAB-LA and SoC model arms



Source: Constructed during the evaluation using data from 'PBAC_March2023_Cabotegravir_Section3_supplement.xlsx'

CAB-LA = cabotegravir- LA; HIV = human immunodeficiency virus; SoC = Standard of care.

Note: Cycle represents 0.5 years.

6.75 The trace shows a greater proportion of individuals being diagnosed with HIV earlier in the SoC arm compared to the CAB-LA arm. This was consistent with the clinical claim. However, as described in paragraph 6.56, this effect was likely overestimated.

6.76 The model was sensitive to the estimate of relative risk of HIV infection in CAB-LA versus SoC, which was based on an indirect comparison. The base case substantially favoured CAB-LA. As discussed in paragraph 6.56, it was unclear whether it was

reasonable to conclude that CAB-LA was superior to TD/FTC in the Australian setting. During the evaluation, sensitivity analyses were conducted which assumed that CAB-LA had the same reduction in risk of infection against SoC as TD/FTC did in the meta-analysed scenarios presented for the indirect comparison (see Table 7). Specifically, the CAB-LA versus SoC risk reduction was assumed to be 0.26 (the risk reduction for TD/FTC over SoC in the meta-analysis of iPrEx, PROUD and IPERGAY) and 0.14 (reflecting the reduction for TD/FTC versus SoC in the meta-analysis of PROUD and IPERGAY), compared to the base case value of 0.088. These sensitivity analyses led to increases in the ICER by 61.6% and 16.0% to \$35,000 to < \$45,000/QALY and \$25,000 to < \$35,000/QALY, respectively. The ESC advised that an assumption of non-inferiority of CAB-LA to TD/FTC within the economic model may be more appropriate than the assumption of superiority. The Pre-PBAC Response reiterated the indirect estimate of effect for CAB vs SoC was derived from the treatment effect of CAB-LA vs TD/FTC observed in HPTN-083 and the meta-analysis of key TD/FTC vs SoC trials, and maintained the effect estimates used in the economic model were reasonable, and perhaps conservative as it was at the lower end of published estimates of CAB-LA effectiveness (ranging from 90-95%) from various studies using meta-regression or other modelling techniques^{19, 20,21}.

- 6.77 One of the key pathways via which inputs impacted the cost-effectiveness was by changing the accrued incremental costs of ART in the model by either reducing time spent on ART (time horizon) or the difference between arms of individuals using ART (treatment effect, baseline HIV risk). The model was also sensitive to changing ART costs directly and changing transition probabilities that affected mortality at lower CD4 health states (and changing time on ART). Increasing ART unit costs by 30% reduced the ICER by 45% and decreasing ART unit costs by 30% increased the ICER by 45%. Removing the assumption of increased mortality in lower CD4 states reduced the ICER by 73% to \$5,000 to < \$15,000/QALY.
- 6.78 Overall, the evaluation considered the estimates of excess mortality by CD4 state were probably reasonable and may possibly have been conservative.

¹⁹ Mitchell KM, Boily MC, Hanscom B, et al. Estimating the impact of HIV PrEP regimens containing long-acting injectable cabotegravir or daily oral tenofovir disoproxil fumarate/emtricitabine among men who have sex with men in the United States: a mathematical modelling study for HPTN 083. *Lancet Reg Health Am.* 2023;18:100416. Published 2023 Jan 17.

²⁰ Smith J, Bansi-Matharu L, Cambiano V, et al. Predicted effects of the introduction of long-acting injectable cabotegravir pre-exposure prophylaxis in sub-Saharan Africa: a modelling study. *Lancet HIV.* 2023;10(4):e254-e265.

²¹ Jamieson L, Johnson LF, Nichols BE, et al. Relative cost-effectiveness of long-acting injectable cabotegravir versus oral pre-exposure prophylaxis in South Africa based on the HPTN 083 and HPTN 084 trials: a modelled economic evaluation and threshold analysis. *Lancet HIV.* 2022;9(12):e857-e867.

- 6.79 Utility values were sourced from Tengs (2002). A utility value of 1.0 was applied to the HIV-free health states. The utility values applied in the economic model are the same as those used in the Kirby model which supported the PBS listing of oral PrEP.
- 6.80 The utility values for individuals treated with CAB-LA do not include any disutility for AEs. The submission considered that this is consistent with the favourable and manageable safety profile of CAB-LA. The submission also considered that it is consistent with PBAC's previous consideration of TD/FTC. Specifically, that the PBAC considered a claim of superior effectiveness and non-inferior safety for TD/FTC plus SoC relative to SoC was reasonable (paragraph 7.10, TD/FTC, PSD, July 2017 PBAC meeting).
- 6.81 The model was sensitive to reducing the utility of HIV negative CAB-LA individuals to 0.99 or 0.98 (e.g. due to ISRs associated with CAB-LA). No disutility associated with adverse events in CAB-LA in the base case was assumed, which may have been unreasonable. However, applying a utility of 0.98 to all HIV negative individuals across both arms had only a minor impact on the ICER. Sensitivity analyses for the utility values of HIV positive health states only had a minor impact on the ICER. The Pre-PBAC Response argued that applying a disutility for injection site reactions was inconsistent with the advice of the ESC that the claim of an acceptable and manageable safety profile was likely to be reasonable (see 'Clinical claim'). The Response presented sensitivity analyses based on applying a disutility of 0.01 in the proportion of patients with any grade ISR events between treatment arms in HPTN-083 (44.5%) for the entire duration of CAB treatment, which increased the base case ICER by 6% from \$15,000 to < \$25,000 to \$15,000 to < \$25,000 per QALY.
- 6.82 Key drivers of the model are summarised in Table 11.

Table 11: Key drivers of the model

Description	Method/Value	Impact Base case: \$ ¹ /QALY gained.
Time horizon	Life-time (63 years) time horizon in the model base case versus a maximum of 153 weeks of blinded study in the HPTN-083 trial.	High, favours CAB-LA Reducing the time horizon to 14 years increases the ICER by 754% to \$ ² /QALY gained.
Background risk	1.4 per 100 person years based on DUSC report.	High, uncertain but may favour CAB-LA Reducing background infection risk to 1.0 increases the ICER by 89% to \$ ³ /QALY gained. Increasing background infection risk to 1.8 reduces the ICER risk 48.6% to \$ ⁴ /QALY gained.
Treatment effect	Based on the indirect comparison of HPTN-083 and meta-analysed values of iPrEx, PROUD and IPERGAY (0.088).	High, favours CAB-LA. Reducing the relative risk reduction to 0.26 increases the ICER by 61.6% to \$ ³ /QALY gained.
Adverse event disutility	None assumed in baseline for CAB-LA	Moderate, favours CAB-LA. Assuming a 0.01 and 0.02 disutility in HIV-negative individuals in the CAB-LA arm (as a proxy for adverse events) increases the ICER by 15.8% and 37.4%, respectively. The scenario in the pre-PBAC Response which applied a disutility of 0.01 to 44.5% of patients based on ISR events in HPTN-083 for the duration of CAB treatment increased the base case ICER by 6% to \$ ¹ /QALY gained.

Source: Table 77, pp175-177 of the submission.

ART = antiretroviral therapy; CAB-LA = cabotegravir long acting; DUSC = Drug utilisation sub-committee; ICER = incremental cost-effectiveness ratio; ISR = injection site reaction; PBS = Pharmaceutical Benefits Scheme; QALY = quality adjusted life year.

The redacted values correspond to the following ranges:

¹ \$15,000 to < \$25,000

² \$155,000 to < \$255,000

³ \$35,000 to < \$45,000

⁴ \$5,000 to < \$15,000

6.83 The results of the stepped economic evaluation are presented in Table 12.

Table 12: Results of the stepped economic evaluation

Step and component	CAB-LA	SoC	Increment
Step 1: Trial-based economic evaluation based on HPTN 083 versus oral PrEP			
Costs	NR	NR	\$
Infection avoided	NR	NR	0.0082
Incremental cost/extra infection avoided			\$ ¹
Step 2: Applicability step: Introduce Australian incidence of HIV versus oral PrEP			
Costs	NR	NR	\$
Infection avoided	NR	NR	0.0024
Incremental cost/extra infection avoided			\$ ²
Step 3: Applicability step: Introduce indirect comparison versus SoC			
Costs	NR	NR	\$
Infection avoided	NR	NR	0.0128
Incremental cost/extra infection avoided			\$ ³
Step 4: Introduce modelled discontinuation, all-cause mortality and discontinuations			
Costs	NR	NR	\$
Infection avoided	NR	NR	0.0111
Incremental cost/extra infection avoided			\$ ³
Step 5: Extrapolation step: Lifetime horizon			
Costs	NR	NR	\$
Infection avoided	NR	NR	0.0264
Incremental cost/extra infection avoided			\$ ⁴
Step 6: Transformation step: Translate HIV infection to costs and QALYs (incl excess mortality)			
Costs	\$	\$45,130.03	\$
QALYs gained	16.8939	16.6856	0.2083
Incremental cost/extra QALY gained (base case)			\$⁵

Source: Table 73, p172 of the submission.

CAB-LA = cabotegravir long acting; SoC = standard of care; NR = not reported; PrEP = pre-exposure prophylaxis; QALY = quality adjusted life year

Note: the submission did not report costs and outcomes for CAB-LA and SoC in the stepped analysis, and these could not be replicated during the evaluation using TreeAge software.

The redacted values correspond to the following ranges:

¹ \$355,000 to < \$455,000

² > \$1,055,000

³ \$255,000 to < \$355,000

⁴ \$455,000 to < \$555,000

⁵ \$15,000 to < \$25,000

6.84 The results of key univariate and multivariate sensitivity analyses are summarised in Table 13.

6.85 The unit costs for ARTs used in HIV treatment in the economic model had changed since the submission, with a small decrease across a range of ARTs. Using the May 2023 DPMQs for the ARTs used for HIV treatment increased the ICER by 4% and have been presented as a sensitivity analysis (Table 13).

Table 13: Key sensitivity analyses around economic evaluation

Analyses		Incremental costs (\$)	Incremental QALY	ICER	% change to ICER
Base case			0.2083	█ ¹	0%
Discount rate (base case: 5% costs and outcomes)	0% costs and outcomes		0.8649	█ ²	-98%
	3.5% costs and outcomes		0.3055	█ ³	-45%
Time horizon (base case: 63 years)	14 years		0.0385	█ ⁴	754%
	20 years		0.0710	█ ⁵	262%
	30 years		0.1344	█ ⁶	54%
Background infection rate of HIV (base case: 1.4 per 100 person years.)	95% LCI (1 per 100 person years)		0.1554	█ ⁷	89%
	95% UCI (1.8 per 100 person years)		0.2568	█ ³	-49%
Duration of HIV risk (base case: life time)	40 years		0.2085	█ ¹	-1%
	30 years		0.2097	█ ¹	-3%
	20 years		0.2137	█ ¹	-11%
	10 years		0.2179	█ ¹	-26%
	3 years		0.1624	█ ¹	-28%
	2 years		0.1349	█ ¹	-21%
	1 year		0.0960	█ ¹	-1%
CAB-LA efficacy RR vs SoC (base case: 0.088)	0.19 (iPrEx)		0.1843	█ ⁶	33%
	0.048 (PROUD/IPERGAY)		0.2178	█ ¹	-11%
	Assuming non-inferior efficacy to TD/FTC (0.26)		0.1679	█ ⁸	62%
	Assuming non-inferior efficacy to TD/FTC (0.14)		0.1960	█ ⁶	16%
Proportion discontinuing (base case: 1st cycle = 0.117, 2nd and subsequent cycles = 0.26)	No discontinuation		0.9179	█ ⁶	48%
Increased HIV mortality by CD4 cell count (base case: Lim (2022))	No increase due to HIV mortality		0.0985	█ ³	-73%
HIV testing and monitoring (base case: 100% increment over SoC)	No incremental testing costs over SoC		0.2083	█ ³	-39%
Cost of HIV ART unit costs (base case: Lim (2022) and updated PBS costs)	Increased by 30%		0.2083	█ ³	-45%
	Decreased by 30%		0.2083	█ ⁶	45%
	Updated to May 2023		0.2083	█ ⁶	4%
Utility values (base case: HIV-negative CAB-LA = 1.00)	0.99		0.1799	█ ⁶	16%
	0.98		0.1515	█ ⁶	37%
Multivariate sensitivity analyses					
14 year time horizon and CAB-LA efficacy = 0.14			0.0362	█ ⁴	839%
14 year time horizon and CAB-LA efficacy = 0.26			0.0311	█ ⁸	1080%
Background risk of HIV (1.0 per 100 person years) & TD-FTC efficacy = 0.14			0.1463	█ ⁹	111%
Background risk of HIV (1.0 per 100 person years) & TD-FTC efficacy = 0.26			0.1255	█ ¹⁰	172%

Source: Table 77, pp175-177 of the submission.

ART = antiretroviral therapy; CAB-LA = cabotegravir long-acting; HIV = human immunodeficiency virus; ICER = incremental cost-effectiveness ratio; LCI = lower confidence interval; pa, per annum; PrEP = pre-exposure prophylaxis; RR = risk reduction; SoC = standard of care; UCI = upper confidence interval.

The redacted values correspond to the following ranges:

¹ \$15,000 to < \$25,000

² \$0 to <\$5,000

³ \$5,000 to < \$15,000

⁴ \$155,000 to < \$255,000

⁵ \$75,000 to < \$95,000

⁶ \$25,000 to < \$35,000

⁷ \$35,000 to < \$45,000

⁸ \$255,000 to < \$355,000

⁹ \$45,000 to < \$55,000

¹⁰ \$55,000 to < \$75,000

- 6.86 The submission included sensitivity analyses around ‘compliance’ to CAB-LA. However these changed only the cost of CAB-LA with no corresponding change in efficacy and therefore was considered not informative.
- 6.87 During the evaluation, multivariate sensitivity analyses were conducted regarding combinations of a reduced time horizon (14 years) and estimates of reduced efficacy consistent with a claim of non-inferior efficacy to oral TD/FTC (but superior to SoC) as well as more conservative estimates of background HIV risk. These sensitivity analyses were selected due to the high sensitivity to time horizon, which was likely too long, treatment effect, which was overestimated, and background risk, which was highly uncertain but may have been overestimated. These sensitivity analyses increased the ICER between 111% (i.e. double) to over 1,000% (i.e. ten-fold), suggesting that the submission may have substantially underestimated the ICER.
- 6.88 For every 1,000 individuals treated with CAB-LA for an average of 3.2 years versus SoC and followed up for 63 years, the economic evaluation (using undiscounted costs and outcomes) estimated that there would be:
- Additional drug cost of \$1 for CAB-LA, compared with SoC;
 - An additional \$3.38 million for drug administration and testing;
 - 26 HIV infections avoided (461 in the SoC arm and 435 in the CAB-LA arm), and a delay of infections which would save \$13.26 million dollars in total treatment, management and hospitalisation costs, be associated with improved quality of life, and result in an average of 719 life-years gained.
 - A reduction in total costs of ART for HIV positive individuals of \$11.98 million;
 - A reduction in HIV disease management costs of approximately \$862,000 compared to SoC;
 - A reduction of other prophylaxis drug costs of \$392,000 compared to SoC; and
 - A reduction in hospitalisation costs of \$23,000 compared to SoC.
- 6.89 Overall, the evaluation considered the ICER presented in the submission was uncertain, due to issues associated with the estimation of the incremental benefit from CAB-LA as PrEP compared to SoC in individuals in whom TD/FTC is contraindicated, or individuals who are intolerant or have reported of suboptimal adherence to TD/FTC (see paragraphs 6.54 to 6.56). There were additional

uncertainties regarding the background rate of HIV infection in the SoC population and the assumption of a constant risk of HIV infection, unadjusted for age. However, there is a paucity of data of the risk of HIV infection in individuals in whom TD/FTC was contraindicated or who are intolerant or have reported suboptimal adherence to TD/FTC to allow for a more accurate estimate. Further, there was uncertainty regarding the appropriate time horizon, as a life-time time horizon could possibly be justified given the disease course of active HIV is well informed and that there is more information regarding the impact of PrEP, though the PBAC has previously considered that a 14-year time horizon for TD/FTC as PrEP provided more certainty. The omission of any disutility for AE associated with CAB-LA (compared to SoC) however favoured CAB-LA and was likely to have led to an overestimate in the cost-effectiveness (i.e. underestimated ICER). The ESC considered the model inappropriately did not include any disutility for adverse events associated with CAB-LA treatment.

- 6.90 The PSCR reiterated that the PBAC originally accepted the cost-effectiveness of oral PrEP (versus SoC) at an annual cost of approximately \$2,500 and argued the higher price of approximately \$█ per annum reflects the superior effect of CAB-LA relative to oral PrEP as demonstrated in the HPTN-083 trial and the economic model calculates an ICER which is similar to that accepted for oral PrEP at \$2,500 per year (i.e. less than \$25,000 to < \$35,000 per QALY). The PSCR acknowledged this ICER is only applicable to the population where SoC is the appropriate comparator and argued there is little uncertainty as to whether CAB-LA is cost-effective in the proposed population, however also acknowledged there were uncertainties with ensuring treatment (and expenditure) is appropriately limited to the requested listing population.

Drug Cost/Individual/Year

Table 14: Drug cost per individual for proposed and comparator drugs

	HPTN-083	Economic Model	Financial estimates
Year 1 injections	9 ^a	8 ^b	7.7 ^c
Subsequent year injections		6.5 ^b	6.25 ^c
Mean time on treatment	1.25 years (median) ^d	3.2 years ^e	NA
Cost per injection		\$█	
Cost/individual – Year 1	NA	\$█	\$█
Cost/ individual subsequent years		\$█	\$█
Average cost/ individual	\$█	\$█	NA

Source: p171 of the submission, Table 23, pp66-67 of the submission and sheets 3.1 and 3.c of the attached financial model.

NA = not applicable

a The HPTN-083 trial did not separate average injections by year but described average number of injection visits.

b Discontinuation not considered in reporting of doses in economic model

c The financial estimates adjusted CAB-LA dose with a 96.2% adherence.

d Mean exposure not presented in the submission or HPTN-083. CSR. Median exposure of 457 days converted to years.

e Back calculated from undiscounted total drug costs. (█-█)/█+█

- 6.91 The drug cost per individual in the first year was \$█ based on a DPMQ of \$█ and 6.5 injections in Year 1 (two loading doses in the first four weeks plus an injection every 8 weeks thereafter). Drug costs per individuals in subsequent years was \$█ based on one dose every 8 weeks and a DPMQ of \$█.

6.92 As the submission nominated SoC as the comparator, no comparator drug costs were included.

Estimated PBS Usage & Financial Implications

6.93 This submission was not considered by DUSC.

6.94 The submission took a mixed market share and epidemiological approach to estimating financial impact.

6.95 Table 15 presents the key inputs relied on in the financial estimates. Given the submission assumed that 94-97% of all individuals who would be eligible for CAB-LA were because they were intolerant to, or have sub-optimal adherence to TD/FTC (as opposed to having contraindications to TD/FTC), the information in Table 15 refers only to uptake in this sub-population.

Table 15: Key inputs for financial estimates

Parameter	Value	Reference/Source and Comments
Non-adherent/Intolerant		
Number of individuals that have previously discontinued TD/FTC (alive and HIV-free)	2024: 45,164 2025: 52,729 2026: 60,460 2027: 68,278 2028: 76,125 2029: 83,960	Kirby Institute 2022, extrapolated over the analysis period. The evaluation considered that the source of estimates was reasonable but included all individuals who ever discontinued TD/FTC without adjusting for individuals who may no longer be at risk and may be overestimated.
Proportion of TD/FTC discontinued individuals eligible for CAB-LA (intolerant or repeated suboptimal adherence)	Base case: 23.8%	HPTN 083 study (Landovitz 2021)
Uptake of CAB-LA	2024: 20% 2025: 22.5% 2026: 25% 2027: 27.5% 2028: 30% 2029: 30%	Assumption based on the proportion of continuous use PrEP users in the DUSC report (MedicineInsight data). The evaluation considered that the application of these estimates for the non-adherent/intolerant population were highly uncertain. While uptake appears substantially underestimated, it is also possible that a large proportion of individuals who are technically eligible for CAB-LA (i.e. ever discontinued TD/FTC) will likely not be seeking PrEP treatment due to changes in circumstance.
PBS Costs		
CAB-LA Scripts	7.70 injections in the first year. 6.25 injections per year thereafter	Based on dosing schedule in HPTN-083 and an adherence of 96.2%. The submission considered that applying 100% adherence to CAB-LA is likely to overestimate financial estimates which is considered inappropriate considering the possibility of a Risk Share Arrangement (RSA). However, no discontinuation was considered in the financial estimates, which was not consistent with the economic evaluation and resulted in an overestimate in CAB-LA use.
ART cost offsets	Sourced from economic model with time horizon set to 6 years.	These were likely overestimated as the economic evaluation overestimated treatment effect of CAB-LA.

Source: Table 93, pp192-193 of the submission.

ABS = Australian Bureau of Statistics; ART = antiretroviral therapy; ASHR2 = Second Australian Study of Health and Relationships; CAB-LA = cabotegravir long-acting; DPMQ = Dispensed price per maximum quantity; DUSC = Drug Utilisation Sub-Committee; GCPS = Gay Community Periodic Surveys; HIV = human immunodeficiency virus; MBS = Medicare Benefits Schedule; MSM = men who have sex with men; PrEP = pre-exposure prophylaxis; TD/FTC = Tenofovir Disoproxil/Emtricitabine.

6.96 Table 16 presents the estimated use and financial implications of listing CAB-LA.

Table 16: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Renal function based contraindication to TD/FTC PrEP	1	1	1	1	1	1
Age-based contraindication to TD/FTC PrEP	1	1	1	1	1	1
Discontinuations due to intolerance or suboptimal adherence	2	2	2	2	2	2
Total eligible individuals	2	2	2	2	2	3
Total individuals treated	6	6	6	6	7	7
Number of scripts dispensed ^a	2	3	3	4	4	5
Estimated financial implications of CAB-LA						
Cost to PBS/RPBS less co-payments	8	8	9	9	9	9
Estimated financial implications for antiretroviral therapy^b						
Cost to PBS/RPBS less co-payments	-3	-3	-3	-3	-3	-3
Cost to PBS/RPBS less co-payments using May 2023 DPMQ for ART offset ^b	-3	-3	-3	-3	-3	-3
Net financial implications						
Net cost to PBS/RPBS	8	8	9	9	9	9
Net cost to PBS/RPBS, May 2023 DPMQ for ART offset ^b	8	8	9	9	9	9
Net cost to MBS	6	6	6	6	6	6
Net cost to Government	9	9	9	9	9	10
Net cost to Government health budgets using May 2023 DPMQ for ART offset	9	9	9	9	9	10

Source: Tables 94 – 96, p194-195, Table 98, pp196-197, Table 100, p198, Table 108, p202 and Table 115, p205 of the submission.

ART = antiretroviral therapy; CAB-LA = cabotegravir – long acting; DPMQ = dispensed price for maximum quantity; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; PrEP = pre-exposure prophylaxis; RPBS = Repatriation Pharmaceutical Benefits Scheme; TD/FTC = Tenofovir Disoproxil/Emtricitabine

^a Assuming 7.7 scripts in first year of treatment and 6.25 in second year as estimated by the submission.

^b As discussed in paragraph 6.84, price of antiretroviral therapies had changed since the submission.

The redacted values correspond to the following ranges:

¹ < 500

² 10,000 to < 20,000

³ 20,000 to < 30,000

⁴ 30,000 to < 40,000

⁵ 40,000 to < 50,000

⁶ 500 to < 5,000

⁷ 5,000 to < 10,000

⁸ \$0 to < \$10 million

⁹ \$10 million to < \$20 million

¹⁰ \$20 million to < \$30 million

6.97 The total cost to the PBS/RPBS of listing CAB-LA was estimated to be \$0 to < \$10 million in Year 1, increasing to \$10 million to < \$20 million in Year 6, and a total of \$70 million to < \$80 million in the first 6 years of listing. After accounting for ART cost offsets, the submission estimated a total net cost to the PBS/RPBS of

\$0 to < \$10 million in Year 1, increasing to \$10 million to < \$20 million in Year 6, for a total of \$70 million to < \$80 million when using May 2023 DPMQ for ART offset.

- 6.98 These estimates should be considered uncertain given:
- The estimated use of CAB-LA in individuals who were eligible for CAB-LA that have discontinued TD/FTC due to intolerance or suboptimal adherence was considered uncertain and represented the vast majority (> 94%) of all eligible individuals;
 - The inclusion of individuals aged 16/17 years as being contraindicated to TD/FTC was likely unreasonable (see Paragraph 3.7);
 - The submission's assumed duration of treatment with CAB-LA does not correctly consider discontinuation or adjust for patients no longer at risk which may overestimate usage; and
 - The offset from ART listing may be overestimated.
- 6.99 The submission did not account for grandfathered individuals. This was consistent with the requested restriction, which did not include a grandfather restriction.
- 6.100 The PSCR argued the inclusion of individuals aged under 18 years as contraindicated to TD/FTC was reasonable as the TGA registration of TD/FTC is only for people aged 18 and over; however, the Pre-PBAC Response acknowledged the view of the ESC and agreed to remove 16-17 year old people in the estimates.
- 6.101 Key sensitivity analyses around the financial estimates are presented in Table 17.

Table 17: Key sensitivity analyses around financial estimates

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Cumulative
Base case	1	1	2	2	2	2	6
Extrapolated new individuals per quarter (base case: 2,327 individuals)							
+10% (2,559 individuals)	1	1	2	2	2	2	6
-10% (2,094 individuals)	1	1	2	2	2	2	6
Proportion of 16 to 17 years old MSM eligible for PrEP (at risk of HIV) (base case: 8.0%)							
0%	1	1	2	2	2	2	6
40%	1	1	2	2	2	2	6
Proportion of the PrEP eligible population with renal contraindication to oral PrEP (base case: 1.35%)							
0%	1	1	2	2	2	2	6
2.69%	1	2	2	2	2	2	7
Proportion of individuals discontinuing TD/FTC PrEP eligible for CAB-LA (base case: 23.8%)							
10%	1	1	1	1	1	1	4
30%	2	2	2	2	2	2	8
Uptake among discontinued TD/FTC PrEP individuals (base case: 20%-30%)							
10% to 20%	1	1	1	1	2	2	5
30% to 40%	2	2	2	2	3	3	9
Discontinuation of CAB-LA as per economic evaluation – 26% after 6 months then 11.7% every 6 months after (base case: 0%)							
Reduce number of doses in year 1 to 5.53 and year 2 onwards to 4.03 ^b	1	1	1	1	2	2	5

Source: Table 116, p207 of the submission.

CAB-LA = cabotegravir long-acting; HIV = human immunodeficiency virus; MSM = men who have sex with men; PrEP = pre-exposure prophylaxis; TD/FTC = Tenofovir Disoproxil/Emtricitabine.

a The applied discontinuation rate is solely for the distribution of individuals between first year and subsequent years of treatment. It does not impact the total number of individuals estimated to be on treatment with CAB-LA each year

b As a proxy for time based discontinuation as applied in economic evaluation, doses have been adjusted to reflect discontinuation. Doses in year 1 calculated as 3.125 doses (estimated number of doses in cycle 1 of economic model, half cycle corrected so adjusted for discontinuation) plus 74% (1 minus 26% discontinuation in cycle 1) of 3.25 doses (estimated number of doses in cycle 2 onwards in model). Doses in year 2 estimated as 3.25 doses × 74% × 88.3% (1 minus 11.7% discontinuation from cycle 2 onwards) plus 3.25 doses × 74% × 88.3%².

The redacted values correspond to the following ranges:

¹ \$0 to < \$10 million

² \$10 million to < \$20 million

³ \$20 million to < \$30 million

⁴ \$30 million to < \$40 million

⁵ \$50 million to < \$60 million

⁶ \$70 million to < \$80 million

⁷ \$80 million to < \$90 million

⁸ \$90 million to < \$100 million

⁹ \$100 million to < \$200 million

Quality Use of Medicines

6.102 The submission did not present any Quality use of medicines (QUM) factors. Key QUM concerns related to CAB-LA listing may include:

- Best practices for mitigating risk of development of resistance;
- Training and education for patients and health care providers regarding managing risk of HIV infection if switching between oral PrEP and CAB-LA or vice versa;

- Discussion around missed dosages and management thereof; and
- Patient management during the optional oral lead-in phase.

Financial Management – Risk Sharing Arrangements

- 6.103 The submission stated that the sponsor was willing to enter into an RSA to mitigate uncertainties associated with uptake within the proposed population and leakage in individuals who would otherwise use oral PrEP.
- 6.104 The submission did not propose any specific details regarding what the Risk Share Arrangement (RSA) would entail, but given the high risk of leakage, an RSA would need to not only account for uptake estimates, but also the uncertainty with the eligible population estimates.
- 6.105 The PSCR acknowledged an RSA would need to account for both uptake estimates and uncertainty associated with the eligible population and stated this could be achieved using the financial estimates which incorporates uptake rates of between 5% and 30%, which would act as a safeguard against uncertainty with respect to the eligible population estimates. The sponsor proposed an RSA whereby PBS use of CAB-LA beyond the maximum estimated uptake rate of 30% would be assumed to represent 'leakage' into a population who could otherwise receive oral PrEP and therefore would rebate use above this threshold to the price of oral PrEP, which at time of the PSCR (May 2023) equalled a rebate of approximately |%.
- 6.106 The pre-PBAC Response acknowledged that it would be appropriate for PBS expenditure to be limited to the estimates that remove 16-17 year old people (Table 17), after which an |% rebate would apply so that the cost of CAB-LA is equivalent to the cost of oral PrEP.

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 General Schedule listing of CAB-LA for HIV PrEP to allow further deliberation on the population who should be eligible for CAB-LA as PrEP and the associated PBS restrictions. In deferring making a recommendation, the PBAC considered CAB-LA was at least as effective as oral TD/FTC for PrEP, and was an important option for people who cannot use TD/FTC or cannot use TD/FTC in an effective manner.
- 7.2 The PBAC noted that in Australia HIV infection rates had trended down significantly over the past 10 years, with strong uptake of oral PrEP since PBS listing following several state-based demonstration studies. The PBAC noted recent estimates from the

Kirby Institute in 2022²² suggested 65-69% of gay and bisexual men (GBM) reporting condomless sex with casual partners are using PrEP, with incidence estimates of HIV infection of 0.09 per 100 person years reported in 2021. The PBAC further noted estimates of the proportion who discontinue PrEP vary from approximately 25% up to 50% with lifestyle and behaviour changes impacting this in addition to safety, tolerability and adherence issues.

- 7.3 The PBAC noted the hearing, as well as comments from individuals, health professionals and organisations, highlighted the clinical need for alternative PrEP options for people with contraindication, intolerance or poor adherence to TD/FTC. The Committee noted the hearing and comments described additional groups for whom CAB-LA would likely be appropriate where TD/FTC is currently not used, or not used optimally, due to various lifestyle factors or privacy concerns. The PBAC noted the comments reinforced the clinical need for CAB-LA as a long-acting option arises from a diverse range of motivations and needs, and its availability should lead to an overall increase in PrEP coverage.
- 7.4 The PBAC considered a broader population than proposed in the submission (contraindicated or repeated reported suboptimal adherence to TD/FTC) should be eligible for CAB-LA. The PBAC considered all individuals who are determined based on a clinical assessment to likely benefit from a long-acting form of PrEP should be eligible for CAB-LA. As such, the PBAC deferred making a recommendation for CAB-LA to seek further Sponsor input regarding the PBS restriction criteria.
- 7.5 The PBAC considered the nominated comparator of SoC, which may include regular testing for HIV infection and other sexually transmitted infections, as well as condom use, was overall reasonable, although acknowledged a subset of the population may take oral PrEP in a sub-optimally adherent manner.
- 7.6 The PBAC noted the submission was based on two randomised trials comparing CAB-LA with TD/FTC (HPTN-083 and HPTN-084), as well as an indirect comparison informed by the HPTN-083 trial and two trials comparing TD/FTC with placebo (as a proxy for SoC) (iPrEx, and IPERGAY) and one trial comparing TD/FTC either immediately or after a deferral period of one year (PROUD) to estimate the effect of CAB-LA versus SoC via the common comparator of TD/FTC. The PBAC noted HPTN-083 was conducted in HIV negative men and transgender women who have sex with men, and HPTN-084 in HIV negative women. The Committee noted the clinical claim and economic analysis were primarily supported by the HPTN-083 trial and considered this was reasonable as advice from the drug utilisation section of the Department had indicated the population identified as female (as indicated in Medicare/PBS records) was approximately 2% of the population currently using PrEP on the PBS.

²² King, J, McManus, H, Kwon, A, Gray, R & McGregor, S 2022, HIV, viral hepatitis and sexually transmissible infections in Australia: Annual surveillance report 2022, The Kirby Institute, UNSW Sydney, Sydney, Australia. <http://doi.org/10.26190/sx44-5366>

- 7.7 The PBAC considered the magnitude of benefit based on the indirect comparison of CAB-LA to SoC was highly uncertain and likely overestimated due to a range of applicability and transitivity issues. The PBAC noted no evidence was available in the requested second line population, and the HPTN-083 trial specifically excluded individuals who had less than 50% adherence to the oral lead-in treatment. The PBAC noted the baseline HIV risk in the countries where the HPTN-083 trial was conducted was likely substantially different to PROUD, IPERGAY and iPrEx (resulting in an exchangeability issue) and higher than in the Australian setting (resulting in an applicability issue). The PBAC noted the superior effectiveness of CAB-LA relative to TD/FTC in HPTN-083 (and HPTN-084) appeared to be driven by sub-optimal adherence in the oral TD/FTC arm and considered that the applicability of the trial results were unknown due to difficulties measuring the adherence rates in the Australian setting with the use of on-demand PrEP regimens potentially being categorised as non-adherence.
- 7.8 The PBAC considered that the claim of superior comparative effectiveness to SoC was reasonable, however considered the claim of superiority over TD/FTC was difficult to assess due to differences between the trial and the Australian setting, including how oral PrEP is used in practice. Overall, the Committee considered a claim that CAB-LA is, at minimum, as effective as TD/FTC would be reasonable, however considered it was difficult to draw conclusions about the magnitude of any potential incremental benefit with the available information.
- 7.9 The PBAC noted the submission claimed CAB-LA had an acceptable and manageable safety profile compared to SoC and considered that while some people may experience injection site reactions with CAB-LA, the available evidence indicated these were typically mild to moderate and CAB-LA was well tolerated. Overall, the PBAC considered the claim of an acceptable and manageable safety profile compared to SoC was adequately supported.
- 7.10 The PBAC noted the base case ICER presented in the submission was \$15,000 to < \$25,000/QALY and that it was sensitive to the estimates for the background risk of HIV and the efficacy of CAB-LA over SoC. The PBAC noted the ESC advice that the background risk of 1.4 HIV cases per 100 person years was likely the best available estimate although it remained highly uncertain, and that the ICER increased to \$35,000 to < \$45,000/QALY when the risk was reduced to 1 case per 100 person years. The PBAC noted the ICER increased to \$35,000 to < \$45,000/QALY if it was assumed that the effectiveness of CAB-LA was the same as that for oral TD/FTC (RR of 0.26). Overall, the PBAC considered the ICER uncertain.
- 7.11 The PBAC noted the sponsor's argument that the proposed cost for CAB-LA of \$ [REDACTED] per patient per year is cost-effective based on a cost of \$2,500 per patient per year being previously accepted as cost-effective for oral TD/FTC versus SoC and the superior efficacy of CAB-LA over TD/FTC. The PBAC considered this frame of reference to be informative however, because the claim of superior effectiveness of CAB-LA over TD/FTC was not accepted (paragraph 7.8), considered the cost-effective price for CAB-

LA versus SoC should be the same as for TD/FTC over SoC i.e. \$2,500 per patient per year.

- 7.12 The PBAC considered the utilisation estimates were highly uncertain due to the subjective nature of the proposed restriction criteria. However, the Committee considered the estimates included in the submission of approximately 500 to < 5,000 individuals in year 1 based on 20% uptake increasing to 5,000 to < 10,000 individuals in year 6 based on 30% uptake to be plausible estimates of the number of individuals likely to benefit from the availability of an alternative form of PrEP. The PBAC considered treatment discontinuation rates should be consistent with those included in the economic model.
- 7.13 The PBAC noted the sponsor proposed a Risk Sharing Arrangement (RSA) to address uncertainty associated with the size of the eligible population and the assumed uptake rates. It was proposed the financial caps for the RSA be based on the estimated PBS/RPBS expenditure for CAB-LA informed by uptake rates of up to 30%. Any expenditure over the caps would be assumed to reflect use in a population who could be effectively treated with oral TD/FTC and therefore a rebate of approximately 1% would be applied such that the resulting cost for CAB-LA is consistent with that for TD/FTC. The PBAC considered the proposed RSA structure to be appropriate noting the restriction criteria are necessarily subjective. The PBAC considered the RSA should be based on the number of treated individuals as outlined in paragraph 7.12.

Outcome:

Deferred

8 Context for Decision

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

9 Sponsor's Comment

ViiV Healthcare will continue to work with the PBAC to progress towards making Apretude available on the PBS for the prevention of HIV.

Addendum to the July 2023 PBAC PSD:

**4.01 CABOTEGRAVIR,
Suspension for injection,
600 mg in 3 mL,
Apretude[®],
ViiV HEALTHCARE PTY LTD.**

10 Purpose

- 10.1 At its July 2023 meeting, the PBAC deferred making a recommendation for the General Schedule listing of CAB-LA for use as PrEP for HIV infection in persons in whom TD/FTC is contraindicated, or persons who are intolerant or have reported suboptimal adherence to TD/FTC, to allow further deliberation on the population who should be eligible (among other matters). Following further discussion with the Sponsor, ViiV Healthcare Pty Ltd, additional information was submitted including a revised restriction, a lower price offer and revised utilisation and financial estimates.

11 Requested listing

- 11.1 The revised listing proposal included a new criterion to replace that originally proposed in the submission: 'Patient must have repeatedly reported adherence to tenofovir disoproxil and emtricitabine as PrEP that is sufficiently suboptimal to compromise both efficacy and patient safety at the time of initiation with this drug'. This was replaced with the revised criterion: 'Patient has demonstrated, or is highly likely to demonstrate, suboptimal adherence to tenofovir disoproxil and emtricitabine as PrEP such that the efficacy of tenofovir disoproxil and emtricitabine would have been or would be compromised'.
- 11.2 A further amendment was proposed relating to the HIV testing criteria. The clinical criterion requiring individuals to have a negative HIV test result no older than 8 weeks or evidence that an HIV test had been conducted, but the result still forthcoming, was changed to: 'Patient must have a negative HIV test result prior to having the latest PBS-subsidised prescription issued, in accordance with applicable PrEP guidelines.'
- 11.3 The revised proposed restriction is presented below with revisions proposed by the sponsor in italics and strikethrough.

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
CABOTEGRAVIR					
Cabotegravir 600 mg/3 mL prolonged-release suspension for injection	\$1,406.74 published price \$█ effective price	1	1	0	Apretude

Category / Program: Section 85 - General Schedule
Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED)
Clinical criteria:
The treatment must be the sole PBS-subsidised therapy for this PBS indication.
AND
Clinical criteria:
Patient must have at least one of the following prior to having the latest PBS-subsidised prescription issued:
(i) A negative HIV test result no older than 8 weeks;
(ii) Evidence that an HIV test has been conducted, but the result is still forthcoming;
<i>Patient must have a negative HIV test result prior to having the latest PBS-subsidised prescription issued, in accordance with applicable PrEP guidelines.</i>
AND
Clinical criteria:
Patient must be contraindicated or intolerant to treatment with tenofovir disoproxil and emtricitabine at the time of initiation with this drug,
OR
Clinical criteria:
Patient must have repeatedly reported adherence to tenofovir disoproxil and emtricitabine as PrEP that is sufficiently suboptimal to compromise both efficacy and patient safety at the time of initiation with this drug.
<i>Patient has demonstrated, or is highly likely to demonstrate, suboptimal adherence to tenofovir disoproxil and emtricitabine as PrEP such that the efficacy of tenofovir disoproxil and emtricitabine would have been, or would be compromised.</i>
Notes: PrEP users who explain they have had suboptimal adherence but are willing and suitable to continue on tenofovir disoproxil and emtricitabine as PrEP, should be offered additional adherence education.
It is advised that individuals have a documented negative HIV-1 result immediately prior to initiating this drug and undergo repeat HIV-1 testing at regular intervals while on this drug for this indication, in accordance with applicable guidelines.
Special Pricing Arrangements apply.

Source: Adapted from the restriction table in 'Requested listing' section, with revisions proposed by the sponsor in italics and strikethrough.

12 Consideration of the evidence

Economic Analysis

- 12.1 An updated economic model was not presented; however, a lower price offer based on an annual treatment cost of \$█ per individual per year was proposed (based on 6.5 injections per year). The resultant effective AEMP per injection of CAB-LA was \$█ (an █% reduction from the proposed AEMP of \$█ in the July 2023 submission).

Table 19: Estimated use and financial implications – revised proposal

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Renal function-based contraindication to TD/FTC PrEP (eligible)	1	1	1	1	1	1
Age-based contraindication to TD/FTC PrEP (eligible)	1	1	1	1	1	1
Discontinuations due to intolerance or suboptimal adherence (eligible)	2	2	2	2	2	2
Total eligible individuals	2	2	2	2	2	3
Total individuals treated	6	6	6	6	7	7
Number of scripts dispensed	2	3	3	4	4	5
Estimated financial implications of CAB-LA						
Cost to PBS/RPBS less co-payments	8	8	9	9	9	9
Estimated financial implications for antiretroviral therapy						
Cost to PBS/RPBS less co-payments (submission)	10	10	10	10	10	10
Cost to PBS/RPBS less co-payments using September 2023 DPMQ ART prices ^a	10	10	10	10	10	10
Net cost to PBS/RPBS using September 2023 DPMQ ART prices ^a	8	8	8	9	9	9
Net cost to MBS	8	8	8	8	8	8
Net cost to Government ^a	9	9	9	9	9	9
Sensitivity analysis – removing age-based contraindication^a						
Number of treated individuals aged <18 years old removed from estimates ^b	1	1	1	1	1	1
Total individuals treated ^c	6	6	6	6	7	7
Net cost to PBS/RPBS ^a	8	8	8	9	9	9
Net cost to Government (less offsets, with MBS costs) ^a	8	9	9	9	9	9

Source: Based on Table 16, with updates and inputs from the revised utilisation and financial estimates spreadsheet, with updated HIV anti-retroviral therapy costs accounted for by the Secretariat

ART = antiretroviral therapy; CAB-LA = cabotegravir – long acting; DPMQ = dispensed price for maximum quantity; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; PrEP = pre-exposure prophylaxis; RPBS = Repatriation Pharmaceutical Benefits Scheme; TD/FTC = Tenofovir Disoproxil/Emtricitabine

^a Revised estimates accounted for by the Secretariat, using September 2023 DPMQ ART prices.

^b Uptake assumptions in the population aged <18 years old were 5% in year 1, 7.5% in year 2 and 10% in years 3-6

^c Consistent with pre-PBAC response for the July 2023 submission, Table 2, p3

The redacted values correspond to the following ranges:

¹ < 500

² 10,000 to < 20,000

³ 20,000 to < 30,000

⁴ 30,000 to < 40,000

⁵ 40,000 to < 50,000

⁶ 500 to < 5,000

⁷ 5,000 to < 10,000

⁸ \$0 to < \$10 million

⁹ \$10 million to < \$20 million

¹⁰ net cost saving

Financial Management – Risk Sharing Arrangements

12.5 The revised proposal maintained the same risk sharing arrangement (RSA) with a rebate applied to utilisation above the financial estimates such that the cost of CAB-LA was the same as oral PrEP.

Table 20: Revised RSA cap proposal (based on updated price offer)

Financial cap year	Year 1	Year 2	Year 3	Year 4	Year 5
Total Individuals	1	1	1	1	2
Total scripts	3	4	4	5	5
Revised offer - Annual PBS spending cap	6	6	7	7	7
Sensitivity analysis – removing individuals aged <18 years old ^a	6	6	6	7	7

Source: Table 2 of the revised proposal

^a Revised estimates accounted for by the Secretariat, using September 2023 DPMQ ART prices.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 5,000 to < 10,000

³ 10,000 to < 20,000

⁴ 20,000 to < 30,000

⁵ 30,000 to < 40,000

⁶ \$0 to < \$10 million

⁷ \$10 million to < \$20 million

13 PBAC Outcome

- 13.1 The PBAC recommended the General Schedule, Authority Required (STREAMLINED) listing of CAB-LA for HIV PrEP, on the basis that the revised restriction and price offer would achieve an equitable and cost-effective listing. The PBAC considered the revised restriction would appropriately allow a simpler clinical assessment of whether an individual is likely to have compromised efficacy with oral PrEP and would experience a benefit from a long-acting injectable alternative. The PBAC noted the financial estimates for CAB-LA should be revised to remove double counting of individuals aged less than 18 years.
- 13.2 The PBAC noted the revised restriction of ‘Patient has demonstrated, or is highly likely to demonstrate, suboptimal adherence to tenofovir disoproxil and emtricitabine as PrEP such that the efficacy of TD/FTC would have been or would be compromised’. The PBAC considered the revised restriction, which allowed clinicians to more broadly determine whether an individual was likely to be at risk of compromised efficacy with TD/FTC as oral PrEP and would therefore benefit from a long acting injectable option, was reasonable and consistent with the advice from members of the ASHM PrEP guidelines committee (see ‘Sponsor Hearing’/paragraph 6.1).
- 13.3 The PBAC noted the clinical criterion requiring individuals to have a negative HIV test result no older than 8 weeks or evidence that an HIV test had been conducted, but the result still forthcoming, was changed to: ‘Patient must have a negative HIV test result

prior to having the latest PBS-subsidised prescription issued, in accordance with applicable PrEP guidelines.’ The PBAC considered this amendment appropriate.

- 13.4 The PBAC recalled at the July 2023 meeting it had considered the cost-effective price for CAB-LA compared with SoC was \$2,500 per person per year based on a frame of reference to the previously accepted cost-effective price for oral TD/FTC compared with SoC (paragraph 7.11). The Committee noted the updated information from the Sponsor offered a reduced-price equivalent to an annual treatment cost of \$| per year (based on 6.5 doses per year and a DPMQ of \$| per dose). The PBAC noted the cost of treatment in the first year would be higher due to the requirement for 8 doses of CAB-LA. In conjunction with the risk sharing arrangement (RSA) (paragraph 11.6), the PBAC considered CAB-LA cost-effective at the price proposed given the alternative manner of administration and long acting nature of CAB-LA was likely to lead to an overall increase in PrEP coverage (paragraph 7.3) and potentially a reduced risk of HIV infection in some individuals compared with oral PrEP.
- 13.5 The PBAC noted the utilisation estimates were the same as included in the July 2023 submission and did not remove the use in adolescents (individuals aged 16/17 years) as had been done in the July 2023 pre-PBAC response. The PBAC considered adolescents should not be accounted for separately in the estimated use as the PBS listings of TD/FTC as PrEP are not subject to age restriction. The PBAC noted the financial estimates had been updated based on the revised price of CAB-LA.
- 13.6 The PBAC reaffirmed its view that the proposed RSA (paragraph 7.13), with use beyond the cap based on the financial estimates to be rebated to the price of TD/FTC, was reasonable.
- 13.7 The PBAC advised that CAB-LA for PrEP is suitable for prescribing by nurse practitioners.
- 13.8 The PBAC recommended that the Early Supply Rule should apply.
- 13.9 The PBAC found that the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022 for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for CAB-LA:
 - a) The PBAC considered the magnitude of treatment benefit of CAB-LA for individuals who have demonstrated, or are highly likely to demonstrate, suboptimal adherence to TD/FTC was uncertain and hence the criteria of providing a substantial and clinically relevant improvement in efficacy was not met;
 - b) The treatment is not expected to address a high and urgent unmet clinical need, as people who cannot use TD/FTC as oral PrEP may manage their personal HIV risk through other means; and
 - c) It was not necessary to make a finding in relation to whether it would be in the

public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

13.10 The PBAC noted this submission is not eligible for an independent review as it received a positive recommendation.

Outcome:

Recommended

14 Recommended listing

14.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
CABOTEGRAVIR 600 mg/3 mL modified release injection, 3 mL vial	NEW	1	1	0	Apretude®

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Level / Method: <input checked="" type="checkbox"/> Authority Required - Streamlined
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.
Condition: Pre-exposure prophylaxis (PrEP) against human immunodeficiency virus (HIV) infection
Indication: Pre-exposure prophylaxis (PrEP) against human immunodeficiency virus (HIV) infection
Treatment Phase: (N/A)
Clinical criteria: Person must have a negative HIV test result prior to having the latest PBS-subsidised prescription issued, in accordance with applicable PrEP guidelines.
AND
Clinical criteria: Person must be contraindicated or intolerant to treatment with tenofovir disoproxil and emtricitabine at the time of initiation with this drug,
OR
Person has demonstrated, or is highly likely to demonstrate, suboptimal adherence to tenofovir disoproxil and emtricitabine as PrEP such that the efficacy of tenofovir disoproxil and emtricitabine would have been, or would be compromised.
Administrative Advice: PrEP users who explain they have had suboptimal adherence but are willing and suitable to continue on tenofovir disoproxil and emtricitabine as PrEP, should be offered additional adherence education.

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

restriction the sponsor will be informed.

15 Context for Decision

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

16 Sponsor's Comment

ViiV Healthcare welcomes the PBAC recommendation to make Apretude available on the PBS for the prevention of HIV.