7.03 LENACAPAVIR, Tablet 300 mg, Pack containing 2 injection sets containing solution for subcutaneous injection 463.5 mg in 1.5 mL Sunlenca®, Gilead Sciences Pty Limited

1 Purpose of submission

1.1 The Standard Re-entry submission requested a Section 100 (Highly Specialised Drugs Program [HSD]), Authority Required (STREAMLINED) listing for lenacapavir (LEN) for the treatment of people with highly multi-drug resistant human immunodeficiency virus type 1 (HIV-1) infection.

1.2 Listing was requested on the basis of a cost-utility analysis of LEN in combination with optimised background regimen (OBR) versus OBR alone.

1.3 Table 1 presents the key components of the clinical issue addressed by the resubmission.

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

Component	Description
Population	HIV-1 patients with highly multi drug resistant HIV who have no more than 2 fully active ARVs remaining from the 4 main classes that can be effectively combined to form a viable regimen. [a]
Intervention	Lenacapavir + OBR
Comparator	Placebo + OBR
Outcomes	Reduction in HIV-1 RNA of ≥ 0.5 log10 copies/mL at 14 days. HIV-1 RNA < 50 copies/mL and < 200 copies/mL through 104 weeks of treatment. Change from baseline in CD4 cells/mm^3. Adverse events.
Clinical claim	Lenacapavir, in addition to OBR, demonstrates superior comparative effectiveness compared with OBR alone (placebo + OBR) in PLWH who are hMDR. Lenacapavir in addition to OBR demonstrates a non-inferior safety profile with OBR alone (placebo + OBR) in PLWH who are hMDR.

Source: Table 1-2, pp3-4 of the resubmission.
ARV = antiretrovirals; HIV = human immunodeficiency virus; hMDR = highly multidrug resistant; OBR = optimised background regimen; PLWH = people living with HIV; RNA = ribonucleic acid.
a Main classes of ARV include Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTIs) and protease inhibitors (PIs)

2 Background

Registration status

2.1 LEN was registered on the Australian register of therapeutic goods (ARTG) on 27 March 2023 for the following indication:

"in combination with other antiretrovirals… for the treatment of adults with multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive anti-viral regimen."

Previous PBAC consideration

2.2 Table 2 presents a summary of key matters of concern from the previous PBAC consideration.

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addresses it
Requested Restriction	A simpler restriction, similar to maraviroc's restriction, would be more practical (paragraph 7.3, LEN PSD, Nov 2022).	Not addressed.
Clinical effectiveness	The composition of the OBR comparator for the indirect treatment comparison (ITC) should be reflective of contemporary Australian clinical practice (paragraph 7.4, LEN PSD Nov 2022).	The resubmission claimed that the composition of contemporary OBR in Australia was validated through the Australian survey (Attachment 1 to the resubmission) and that a revised ITC presented in the resubmission included the most recent trials investigating an intervention in combination with contemporary OBR for the treatment of hMDR HIV. There were substantial differences between the meta-analysed OBR effect estimates and those given by clinical experts, suggesting the estimate may not reflect OBR composition or effect in Australia.
	Other treatments not PBS listed were inappropriately included in the intervention arm (LEN + OBR) of the ITC (paragraph 7.4, LEN PSD Nov 2022).	Not adequately addressed. The resubmission included two additional trials into the OBR comparator arm of the ITC that include newer agents (FTR, IBA, INSTI) in each treatment arm of the ITC (i.e., LEN + OBR and OBR). The resubmission argued that this offset any potential bias observed due to the inclusion of these ARV agents. The evaluation considered this was unlikely to adequately offset potential bias, as the weighting in the resubmission composition analysis and the meta-analysis that was used to inform effect, were inconsistent. Additionally, adding non-PBS listed agents to the meta-analysis means the results are less applicable to the Australian setting.
	The ESC previously considered it was 'more reasonable and reliable to utilise the maximum amount of available data in the economic evaluation; i.e. all Cohort 1 & 2 data' (paragraph 6.44 LEN PSD Nov 2022).	Addressed. The ITC presented in this resubmission is based on combined Cohorts 1 and 2 of LEN + OBR from CAPELLA. This evaluation considered that this was reasonable.
	The randomised period was of uncertain applicability to the proposed population because the comparator during that time was a known failing regimen, rather than OBR (paragraph 7.5, LEN PSD, Nov 2022).	Not addressed.
	Transitivity issues including the small patient numbers in CAPELLA, the lack of a common comparator, and differences in the trial populations regimen or agents used (paragraph 7.6, LEN PSD, Nov 2022).	Partially addressed. The resubmission attempted to balance ARVs used in OBR. However, the ITC remains unanchored with no common comparator and patient numbers (n=72) from the CAPELLA trial remain low.

Component	Matter of concern	How the resubmission addresses it
Safety	The safety claim remained somewhat uncertain due to the small sample size of CAPELLA and the absence of long-term safety data (paragraph 7.7, LEN PSD, Nov 2022).	Addressed. The resubmission provided longer (104 week) follow-up safety data, which did not indicate any new safety signals.
Economics	There was insufficient data in the CAPELLA study (given its small size and limited randomised data) to inform a large 16-health state model with extrapolated benefits over a lifetime (paragraph 7.8, LEN PSD, Nov 2022).	Partially addressed. The resubmission included longer term follow-up from the combined 1&2 cohorts. However, the evaluation considered that this was still likely insufficient to inform a 16-health state model. Additionally, relying on observed CAPELLA KM data up to week 104 led to illogical model transitions.
	The PBAC also considered the incremental cost-effectiveness ratio was unacceptably high at the proposed price (paragraph 7.8, LEN PSD, Nov 2022).	Partially addressed. A lower requested price ([redacted]% reduction) and base case ICER [redacted][1]/QALY) was presented in the resubmission. However, the alternative base case, which preserves the previous model's extrapolation, results in a higher ICER ([redacted][2]/QALY) than the previous submission [redacted][3]/QALY), including the [redacted]% reduction in price.
	Adjustment to the cost-effectiveness analysis should have been made using more conservative treatment effects and an analysis which enables a frame of reference with the cost of other therapies that were originally (or remain) listed as later-line or salvage therapies, such as maraviroc (paragraph 7.10, LEN PSD, Nov 2022).	Partially addressed. The clinical incremental benefit applied to the economic model was lower than in the previous submission (RR = 2.807 vs RR = 3.828), however the evaluation considered the clinical benefit remained optimistic. Further, the modelled treatment effect was inconsistent with the assumption of a lower incremental benefit.
Financials	Financial estimates were uncertain given that the likely uptake in practice was unclear (paragraph 7.9, LEN PSD, Nov 2022).	Partially addressed. The resubmission made some modifications to the budget impact model and provided additional background based on clinician survey responses. However, the model did not alter uptake rates.
	Financial estimates appeared to exclude OBR costs, and given the economic model indicated an additional incremental cost for other ARVs in the lenacapavir arm, considered this was inappropriate (paragraph 7.9, LEN PSD, Nov 2022).	Addressed. However, OBR costs in the financial estimates may be underestimated based on relative cost of OBR and LEN in the economic model.

Source: Table 1-1, pp 2-3 of the resubmission and the Lenacapavir November 2022 PBAC PSD.
ARV = antiretroviral; FTR = fostemsavir; HIV = human immunodeficiency virus; hMDR = highly multidrug resistant; IBA = ibalizumab; ICER = incremental cost-effectiveness ratio; INST = integrase strand transfer inhibitor; ITC = indirect treatment comparison; KM = Kaplan-Meier; LEN = lenacapavir; OBR = optimised background regimen; PBS = Pharmaceutical Benefits Scheme; PSD = public summary document; QALY= quality adjusted life year
The redacted values correspond to the following ranges:
[1] $75,000 to < $95,000
[2] $115,000 to < $135,000
[3] $75,000 to < $95,000

3 Requested listing

3.1 One restriction for all treatment phases, as proposed by the Secretariat is shown below.

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
Lenacapavir					
300mg tablet, 5 tablets per pack	$ [redacted] Published $ [redacted] Effective	1	5	0	Sunlenca
463.5 mg/1.5 mL [309 mg/mL] for SC injection, 2 vials per pack	$ [redacted] Published $ [redacted] Effective	1	2	0	Sunlenca

Category / Program: Section 100 – Highly Specialised Drugs Program {Community Access}
Prescriber type: ☒Medical Practitioners ☒Nurse practitioners
Restriction Level / Method: ☒Authority Required (Streamlined) [code new 2B]
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.
Indication: Human immunodeficiency virus (HIV)
Clinical criteria:
The condition must be resistant (this includes virological failure/clinical failure/genotypic resistance) to multiple drugs to the extent that there are no more than 2 fully active HIV-antivirals remaining from the 4 main antiretroviral classes that could be effectively combined to form a viable treatment regimen.
AND
Clinical criteria:
The treatment must be in addition to optimised background therapy.
Prescribing Instructions: Virological failure is defined as a viral load greater than 200 copies per mL on two consecutive occasions, while clinical failure is linked to emerging signs and symptoms of progressing HIV infection or treatment-limiting toxicity.
Prescribing Instructions: Genotypic resistance to individual anti-retroviral drugs is to be determined by genotypic testing.
Administrative Advice: For the purposes of this restriction, the four main antiretroviral classes include nucleotide/nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INTSIs) and protease inhibitors (PIs).

3.2 The maximum quantity was increased from four tablets in the previous submission to five tablets to account for the TGA approved dose of five tablets (600mg on days 1 and 2, with an additional 300mg tablet on Day 8) compared to the proposed loading dose of four tablets (600mg on days 1 and 2 only).

3.3 The resubmission proposed a reduction in the effective price from $ [redacted] for the oral initiation (4 tablets) and $ [redacted] for 2 vials to $ [redacted] for oral initiation (5 tablets) and $ [redacted] for 2 vials. This was approximately a [redacted]% price decrease for the vials.

3.4 The resubmission incorporated most of the suggested restriction changes from the previous submission. However, the resubmission's updated proposed restriction for LEN defines virologic failure as a viral load greater than 200 copies/mL on two separate occasions, which the resubmission noted aligned with the definition in the ASHM Guidelines (ASHM 2019) and had agreement from Australian clinicians surveyed. The current PBS restrictions for HIV treatments on the PBS have a higher threshold of virologic failure defined as viral load greater than 400 copies/mL on two consecutive

occasions. The ESC considered it was reasonable to define virologic failure consistent with current ASHM guidelines.

3.5 Additionally, the PBAC had considered that a simpler restriction, similar to maraviroc's restriction, 'would be more practical as it frames the number of past treatments in an affirmative manner, whereas the proposed restriction requires a complex exercise of deduction involving a large number of permutations' (paragraph 7.3, lenacapavir, Public Summary Document [PSD], November 2022 PBAC meeting). The resubmission did not change the requested restriction to reflect this consideration and the number of past treatments remain undefined in an affirmative manner. The ESC also considered that a simpler restriction would likely be reasonable for LEN, but acknowledged that due to the late positioning of LEN, it may be difficult to correctly frame the number of past treatments in an affirmative manner accurately.

3.6 A survey of Australian clinicians conducted by the sponsor indicated differences in how clinicians interpreted the proposed clinical criteria for listing. Some considered that the listing would apply to patients with only two fully active agents (from the four main classes) based on genotypical failure. Others considered that the listing would apply to patients with only two fully active agents (from the four main classes) that the patient is able to take i.e. clinical failure and virological failure, in addition to genotypical resistance. One sexual health physician from NSW noted that '(i)t includes aspects of clinical failure that might be related to adherence or tolerability issues as well as actual confirmed virological failure'. The evaluation considered more clarity around eligibility may be necessary in order to minimise usage beyond the requested restriction.

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

4 Population and disease

4.1 HIV is a retrovirus that infects host cells via reverse transcription of its viral ribonucleic acid (RNA) and integration of the resulting viral deoxyribonucleic acid (DNA) into the host's genome (Deeks 2015). Inadequate treatment of HIV infection leads to the depletion of CD4 T cells, the development of AIDS-defining events and, ultimately, death (Deeks 2015). Among patients unable to maintain virologic suppression for long periods of time, there is a subset of people living with HIV (PLWH) who are highly multidrug resistant (hMDR) and they usually have a history of virologic failure on multiple lines of treatment, due to the development of resistance mutations to multiple drug classes. Evidence indicates that there is a higher rate of mortality in PLWH who are highly MDR compared to PLWH who are not highly MDR (Gagliardini 2020; Galli 2020; Mauro 2007; Pelchen-Matthews 2021). The population remains unchanged from the previous submission.

4.2 LEN is a novel HIV-1 capsid inhibitor. The capsid surrounds HIV's genetic material. By binding directly between the capsid protein subunits, LEN inhibits three steps of the

viral lifecycle: capsid-mediated nuclear uptake of HIV proviral DNA, virus assembly and release, and capsid core formation.

4.3 LEN is proposed, in combination with OBR, for the treatment of patients who are highly MDR after development of resistance to multiple regimens, and who have no more than two fully active agents remaining from the four main antiretroviral (ARV) classes (nucleo(s/t)ide reverse transcriptase inhibitors [NRTI], non-nucleoside reverse transcriptase inhibitors [NNRTI], integrase strand transfer inhibitors [INSTI] and protease inhibitors [PI]) that can be effectively combined to form a viable regimen.

4.4 Unlike the previous submission, the resubmission claimed that the 'Rule of Rescue' would apply to individuals who have no fully active ARV available to construct a viable ARV regimen (the resubmission estimated this would apply to a cohort of < 500 patients) based on responses to a survey of 10 clinicians. The evaluation considered this estimate was uncertain. In CAPELLA, 12 out of the 72 enrolled patients (16.7%) had no fully active ARVs in the OBR.

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

5 Comparator

5.1 The resubmission has nominated the same comparator as the previous submission, OBR alone.

5.2 The PBAC previously considered that OBR, as a 'basket of therapies and regimens which may be used in the hMDR population' was a reasonable comparator. However, the composition of the basket should reflect 'contemporary Australian clinical practice' (paragraph 7.4, lenacapavir PSD, Nov 2022 PBAC meeting).

5.3 The resubmission stated that multiple steps had been taken to ensure OBR reflected contemporary Australian clinical practice, including:

- Validation of OBR composition in contemporary Australian clinical practice through a survey/semi-structured interview of 10 Australian clinicians experienced in treating PLWH, including hMDR;
- Updated OBR comparator arm of the indirect treatment analysis (ITC) to include the most recent trials investigating an intervention in combination with OBR in PLWH who are hMDR; and
- Assessment of the impact of OBR agents reflecting contemporary OBR on LEN + OBR arm effectiveness in CAPELLA using subgroup analysis.

5.4 The evaluation considered the steps taken by the resubmission may not have appropriately and sufficiently addressed the issues previously raised by the PBAC regarding the composition of OBR in Australian clinical practice. The ESC noted the PBAC had previously considered the OBR basket should be reflective of Australian clinical practice (paragraph 7.4, lenacapavir PSD, November 2022 PBAC meeting) and considered it was inappropriate for the resubmission to have added ibalizumab (IBA)

and FTR to the comparator as neither ARV are used in contemporary Australian clinical practice, and therefore presents an additional applicability issue to the OBR alone arm which was not present from the previous submission. The Pre-PBAC Response argued the inclusion of IBA and FTR trials in the OBR basket increased the representation of the INSTI class in the OBR arm to a level considered to be consistent with contemporary Australian clinical practice and the reported use in the LEN + OBR arm of the CAPELLA trial. The Response stated the approach was the best available to ensure any impact on efficacy due to FTR and IBA was shared across the ITC treatment arms and therefore the incremental gain for LEN + OBR compared with OBR remained unimpacted by their inclusion. The extent to which these issues are addressed is discussed further in the clinical evidence and clinical effectiveness sections below.

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 clinicians (2) described groups of hMDR patients who would benefit from the addition of a new treatment option with fewer side effects. The clinicians highlighted that the groups of patients who would benefit from the listing of LEN were generally older and diagnosed a relatively long time ago, who had received a range of 'best available' treatments at the time, but because of how early-generation anti-retroviral therapies were used, have developed multi-drug and multi-class resistance. The hearing also described challenges of effective HIV treatment in older patients who are hMDR because of increasing co-morbidities, drug-drug interactions and the severe side effects of long-term treatment for HIV (especially with the protease inhibitor class) and highlighted the benefits LEN would provide for these patients, with its favourable adverse event profile and the ability to rationalise and re-formulate individual patients ART regimens to manage individual circumstances.

Consumer comments

6.2 The PBAC recalled it had previously received input from 1 individual highlighting the need for additional treatment options for people living with highly multi-drug resistant HIV infection (paragraph 6.2, lenacapavir PSD, November 2022 PBAC meeting). The PBAC noted and welcomed the input from health care professionals (1) and from the National Association of People with HIV Australia (NAPWHA) via the Consumer Comments facility on the PBS website. The comment from the health professional highlighted the need for additional treatment options in this highly treatment-experienced group and noted the evidence indicated good activity against drug-resistant HIV. The PBAC also noted the input from NAPWHA stated the organisation was concerned the proposed listing was too narrow, and the addition of an agent with a new mechanism of action with a favourable side effect profile, minimal drug-drug interactions and no food/dosing requirements would make it a useful option for a

broader population of PLWH.

Clinical trials

6.3 The resubmission was based on an unanchored ITC of LEN + OBR versus OBR alone. The ITC relied on the same trials as the previous submission (CAPELLA [N=72], MOTIVATE 1 [N=601], MOTIVATE 2 [N=474], BENCHMRK 1 [N=352], BENCHMRK 2 [N=353], VICTOR-E [N=114]) plus two additional studies (BRIGHTE [N=371] and TMB-301 [N=40]).

6.4 The resubmission also presented updated CAPELLA results from a Week 104 analysis (compared to Week 52 analysis in the previous submission).

6.5 Details of the trials and studies 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
CAPELLA NCT04150068	Gilead Sciences Inc (2019). NCT04150068: Study to Evaluate the Safety and Efficacy of Lenacapavir (GS-6207) in Combination With an Optimized Background Regimen (OBR) in Heavily Treatment Experienced Participants Living With HIV-1 Infection With Multidrug Resistance (GS-US-200-4625).	2019
	Gilead Sciences Inc (2021). GS-US-200-4625: A Phase 2/3 Study to Evaluate the Safety and Efficacy of Long Acting Capsid Inhibitor GS-6207 in Combination with an Optimized Background Regimen in Heavily Treatment Experienced People Living With HIV-1 Infection With Multidrug Resistance: Interim Clinical Study Report Addendum (week 52 data).	2021
	Key Publication Segal-Maurer, S, DeJesus, E, et al. Capsid Inhibition with Lenacapavir in Multidrug-Resistant HIV-1 Infection.	The New England journal of medicine 2022; 386(19): 1793-1803.
	Margot, N, Vanderveen, L, et al. Phenotypic resistance to lenacapavir and monotherapy efficacy in a proof-of-concept clinical study	The Journal of antimicrobial chemotherapy 2022; 77(4): 989-995.
Comparator trials		
BENCHMRK (1 and 2) NCT00293267	Steigbigel, RT, Cooper, DA, et al. Raltegravir with optimized background therapy for resistant HIV-1 infection.	The New England journal of medicine 2008; 359(4): 339-354.
	Merck Sharp & Dohme LLC NCT00293267: A Study to Evaluate the Safety and Efficacy of Raltegravir (MK0518) in HIV-Infected Patients Failing Current Antiretroviral Therapies (MK0518-018 EXT2).	
	Merck Sharp & Dohme LLC NCT00293254: A Study to Evaluate the Safety and Efficacy of Raltegravir (MK0518) in HIV-Infected Patients Failing Current Antiretroviral Therapies (0518-019	
	Cooper, DA, Steigbigel, RT, et al. Subgroup and resistance analyses of raltegravir for resistant HIV-1 infection.	The New England journal of medicine 2008; 359(4): 355-365
	Steigbigel, RT, Cooper, DA, et al. Long-term efficacy and safety of Raltegravir combined with optimized background therapy in treatment-experienced patients with drug-resistant HIV infection: week 96 results of the BENCHMRK 1 and 2 Phase III trials."	Clinical infectious diseases 2010; 50(4): 605-612.
	Eron, JJ, Cooper, DA, et al. Efficacy and safety of raltegravir for treatment of HIV for 5 years in the BENCHMRK studies: final results of two randomised, placebo-controlled trials.	The Lancet. Infectious diseases 2013; 13(7): 587-596.

Trial ID	Protocol title/ Publication title	Publication citation
MOTIVATE (1 and 2) NCT00098722	Gulick, RM, Lalezari, J, et al. Maraviroc for previously treated patients with R5 HIV-1 infection.	The New England journal of medicine 2008; 359(14): 1429-1441.
	ViiV Healthcare NCT00098722: Trial of Maraviroc (UK-427,857) in Combination With Optimized Background Therapy Versus Optimized Background Therapy Alone for the Treatment of HIV-1 Infected Subjects (MOTIVATE 2).	
	ViiV Healthcare and Pfizer NCT00098306: Trial of Maraviroc (UK-427,857) in Combination With Optimized Background Therapy Versus Optimized Background Therapy Alone for the Treatment of HIV-1 Infected Subjects (MOTIVATE 1)	
	Asmuth, DM, Goodrich, J, et al. CD4+ T-cell restoration after 48 weeks in the maraviroc treatment-experienced trials MOTIVATE 1 and 2.	Journal of acquired immune deficiency syndromes 2010; 54(4): 394-397.
	Fatkenheuer, G, Nelson, M, et al. Subgroup analyses of maraviroc in previously treated R5 HIV-1 infection.	The New England journal of medicine 2008; 359(14): 1442-1455
	Gulick, RM, Fatkenheuer, G, et al. Five-year safety evaluation of maraviroc in HIV-1-infected treatment-experienced patients.	Journal of acquired immune deficiency syndromes 2014; 65(1): 78-81.
	Hardy, WD, Gulick, RM, et al. Two-year safety and virologic efficacy of maraviroc in treatment-experienced patients with CCR5-tropic HIV-1 infection: 96-week combined analysis of MOTIVATE 1 and 2.	Journal of acquired immune deficiency syndromes 2010; 55(5): 558-564.
	Nelson, M, Fisher, M, et al. Impact of baseline antiretroviral resistance status on efficacy outcomes among patients receiving maraviroc plus optimized background therapy in the MOTIVATE 1 and 2 trials.	HIV clinical trials 2010; 11(3): 145-155.
	van Lelyveld, SFL, Wensing, AMJ, et al. The MOTIVATE trials: maraviroc therapy in antiretroviral treatment-experienced HIV-1-infected patients.	Expert review of anti-infective therapy 2012; 10(11): 1241-1247
VICTOR-E NCT00243230	Suleiman, J, Zingman, BS, et al. Vicriviroc in combination therapy with an optimized regimen for treatment-experienced subjects: 48-week results of the VICTOR-E1 phase 2 trial.	The Journal of infectious diseases 2010; 201(4): 590-599.
	Merck Sharp & Dohme LLC NCT00243230: Vicriviroc (SCH 417690) in Combination Treatment With Optimized ARV Regimen in Experienced Participants (VICTOR-E1) (MK-7690-020/P03672) (VICTOR-E1).	
BRIGHTE NCT02362503	Kozal, M., J. Aberg, G. Pialoux, P. Cahn, M. Thompson, J.-M. Molina, B. Grinsztejn, R. Diaz, A. Castagna, P. Kumar, G. Latiff, E. DeJesus, M. Gummel, M. Gartland, A. Pierce, P. Ackerman, C. Llamoso, M. Lataillade and B. T. Team. Fostemsavir in Adults with Multidrug-Resistant HIV-1 Infection.	The New England journal of medicine 2020; 382(13): 1232-1243.
	ViiV Healthcare. NCT02362503: Attachment Inhibitor Comparison in Heavily Treatment Experienced Patients.	2015
	Ackerman, P, Thompson, M, et al. Long-term efficacy and safety of fostemsavir among subgroups of heavily treatment-experienced adults with HIV-1.	AIDS 2021 (London, England) 35(7): 1061-1072.
	Gartland, M, Cahn, P, et al. Week 96 Genotypic and Phenotypic Results of the Fostemsavir Phase 3 BRIGHTE Study in Heavily Treatment-Experienced Adults Living with Multidrug-Resistant HIV-1.	Antimicrobial agents and chemotherapy 2022; 66(6): e0175121
	Emu B, Fessel J, Schrader S, et al. Phase 3 Study of Ibalizumab for Multidrug-Resistant HIV-1.	The New England journal of medicine 2018; 379(7): 645-54

Trial ID	Protocol title/ Publication title	Publication citation
TMB-301 NCT02475629	Mascolini M. Two Thirds Reach Sub-50 Viral Load Through 48 Weeks With Ibalizumab. TaiMed Biologics Inc. NCT02475629: Ibalizumab Plus Optimized Background Regimen in Patient With Multi-Drug Resistant HIV.	HIV Drug Therapy, 2018; Glasgow 2015

Blue shaded cells represent trials previously considered by the PBAC.
Source: Table 2-4, pp41-44 of the resubmission.

6.6 The key features of the included evidence are summarised in Table 4.

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

Trial/ cohort	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Lenacapavir + OBR versus Placebo + OBR CAPELLA trial						
LEN + OBR (cohort 1A)	24	R, DB/OL 14 days/ 52 weeks [a]	Unclear [b]	HIV patients – Resistance to ≥ 2 ARV medications from each of ≥ 3 of the 4 main classes of ARV medications (NRTI, NNRTI, PI, INSTI).	HIV-1 RNA levels < 50 copies/mL and < 200 copies/mL at week 52. Change from baseline in CD4 cells/mm3	Yes
PBO + OBR (Cohort 1B)	12					
LEN + OBR + cohort 2	36	OL 52 weeks				
Included trials for indirect comparison (OBR arms)						
BENCHMRK 1	352	R, DB, Phase 3	Low	HIV patients -Resistance to at least 1 drug in each of 3 classes of oral ARVs (NRTI, NNRTI, PI)	Patients with a HIV-1 RNA levels < 50 copies/mL at week 4; patients with a viral load < 400 copies/ mL at week 48	RR of meta-analysed virologic suppression results applied to the model
BENCHMRK 2	353					
MOTIVATE 1	601	R, DB, Phase 2/3	Low	Had taken ≥1 ARVS from 3 ARV classes (NRTI, NNRTI, at least 2 PIs or fusion inhibitors) for ≥ 6 months or had documented phenotypic or genotypic resistance to drugs from at least 3 of these classes		
MOTIVATE 2	474					
VICTOR- E	114	R, DB	Low	Resistance mutation to the NRTI class and ≥ 1 primary resistance mutation to the PI class		
BRIGHTE FTR + OBR	203	R, DB/OL 7 days/96 weeks	Unclear	ARV-experienced with documented historical or baseline resistance, intolerability, and/or contraindications to ARVs in ≥ 3 classes.	Patients with HIV-1 RNA levels < 40 copies/mL, n (%) at 48 weeks	
BRIGHTE PBO + OBR	69					
BRIGHTE FTR + OBR	99	OL, 96 weeks				
TMB-301	40	SAS, OL, 25 weeks	High	Resistance to ≥ 1 ARV medication from each of 3 classes of ARV medications as measured by resistance testing.	Patients with HIV-1 RNA levels < 50 copies/mL, n (%) at 25 weeks	

Source: Table 3, p10 of Lenacapavir November 2022 PBAC PSD and pp51 – 92 of the resubmission.
Blue shaded cells represent trials previously considered by the PBAC.
ARV = antiretroviral; DB = double blind; FTR = fostemsavir; HIV = human immunodeficiency virus; INSTI = integrase strand transcriptase inhibitors; LEN = lenacapavir; MC = multi-centre; NNRTI = non-nucleoside reverse transcriptase inhibitors; NRTI = nucleo(s/t)ide reverse transcriptase inhibitors; OBR = optimised background regimen; OL = open label; OS = overall survival; PBO = placebo; PFS = progression-free survival; PI = protease inhibitor; R = randomised; RNA = ribonucleic acid; SAS = single arm study.
[a] As per FDA guidance, the trial consisted of a 14-day randomised double blind phase followed by 52-week OL phase where all patients switched to LEN + OBR.
[b] The randomised 14-day comparison in Cohort 1 generally had a low risk of bias, but the clinical claim is primarily based on long term non-comparative open-label data. It is unclear overall what the risk of bias is for the trial as a whole.

6.7 The initial 14-day functional monotherapy period of CAPELLA overall had a low risk of bias. However, a major part of the clinical claim is based on data after the initial 14-day period, where results were open label and had no control group, which, based on the Cochrane risk of bias tool, is high risk of bias, suggesting an unclear risk of bias overall. The PBAC previously noted the additional risk of bias in the CAPELLA trial beyond 14 days due to its open label nature, however considered this risk was mitigated somewhat by the primary outcomes of viral load and CD4 counts being serologically measured (paragraph 6.7, lenacapavir PSD, November 2022 PBAC meeting).

6.8 For the November 2022 submission it was noted that '(a)ll of the comparator trials (BENCHMRK 1 & 2, MOTIVATE 1 & 2, VICTOR-E) were adequately randomised and double blind, with low risk of reporting and attrition bias, and overall had low risks of bias within each trial. However, as the submission included only the single treatment arms of interest in the clinical evaluation by the resubmission, the risk of bias from using data from only the comparators in these trials should be considered high as the benefits of randomisation for the respective trials were not retained' (paragraph 6.12, Lenacapavir PSD, November 2022 PBAC meeting).

6.9 Similar to CAPELLA, BRIGHTE included an 8-day randomised, placebo-controlled functional monotherapy period where FTR or placebo were added to failing ARV, followed by a longer-term phase where all patients received FTR and OBT (i.e., OBR). In addition, BRIGHTE had a separate, non-randomised cohort where all patients received FTR plus OBR for 96 weeks. Overall, the evaluation considered that the risk of bias in BRIGHTE was similar to that of CAPELLA, with the initial randomisation period (eight days) having a low risk of bias and the later open label periods, on which the ITC is based, having a high risk of bias and unclear risk of bias overall.

6.10 In BRIGHTE, the threshold for undetectable viral load was < 40 copies/mL, which the resubmission assumed to be equal to a threshold of < 50 copies/mL in the ITC. The evaluation considered that it was unclear to what extent this would bias results of the ITC, but the more stringent definition of undetectable viral load may bias in favour of LEN.

6.11 TMB-301 was a non-comparative single arm study. The resubmission noted it had a 7-day baseline period, then the IBA loading dose was given (2000 mg intravenous [IV]) with failing ARV for seven days and then maintenance IBA (800 mg IV every 14 days) in combination with OBR was commenced. The study duration was 25 weeks, and there was no longer-term extension study which included all patients of TMB-301 out to 48/52 weeks. The resubmission claimed that even though there were some published details reported for some of the patients who were eligible for a continuation phase, outcomes were not reported for all patients and therefore could not be used. As such, the resubmission assumed that similar viral load undetectability was achieved at Week 48/52 as reported at 25 weeks.

6.12 The evaluation considered that overall, as a non-comparative study, TMB-301 would have a high risk of bias and the assumption of the 25-week result applying to 48/52 weeks further increased the risk of bias. While incomplete, available results for the 27 patients at week 48 (compared to 40 patients at week 25) reported for TMB-301 in Mascolini 2018 indicated a response rate of 67% (compared to 43% at week 25). Using the week 25 response rate to inform week 48 results may potentially underestimate response to IBA and would lower the incremental effect estimated in the ITC, favouring LEN. It is possible that the higher response rate was influenced by attrition bias. The Pre-Sub-Committee Response (PSCR) stated the 67% response rate was an incomplete efficacy analysis response rate for the extension phase and was not an intention-to-treat (ITT) population analysis. Furthermore, it only included 27/40 patients and as the initial phase ceased at 25 weeks, patients for whom there was no data were assumed to be treatment successes for analyses beyond this point. The Response therefore argued the use of the ITT response rate at 25 weeks was reasonable.

6.13 The resubmission claimed that to address the imbalances in use of INSTIs and newer agents between LEN + OBR (in CAPELLA) and OBR alone (from the comparator studies), BRIGHTE and TMB-301 trials were included in the meta-analysis of OBR alone. The resubmission claimed this introduced a proportion of FTR and IBA use consistent with their use forming OBR in the LEN + OBR arm of CAPELLA.

6.14 The evaluation considered that the inclusion of BRIGHTE and TMB-301 may not be justified as neither IBA nor FTR is available on the PBS and none of the Australian clinicians surveyed by the sponsor indicated that they use IBA or FTR in any HIV patients. While the resubmission argued that the inclusion of BRIGHTE and TMB-301 in the comparator would allow adjustments for the use of IBA and FTR in the LEN + OBR arm, it would misrepresent the response rate of OBR alone in Australian practice. Further, this approach assumed that there was no synergistic benefit between IBA or FTR with LEN, which may not be appropriate given that different ARVs with different mechanisms of actions are commonly used as there is synergy between classes.

6.15 The PSCR argued the FTR and IBA trials are the most contemporary studies to investigate an intervention, in combination with OBR, in hMDR patients living with HIV, and argued the composition of OBR in these trials largely reflects contemporary clinical practice given all medicines are available and used in Australia (except for FTR and IBA themselves). The Response further argued that as more recent trials, the increased use of INSTIs in the OBR composition of these studies should more appropriately reflect utilisation in Australian practice, and their inclusion resulted in more consistency in the OBR in the comparator arm and the LEN + OBR arm of CAPELLA.

Comparative effectiveness

6.16 The primary outcome of CAPELLA was the proportion of patients with a reduction in HIV-1 RNA of ≥ 0.5 $\log_{10}$ copies/mL from baseline at the end of the 14-day Functional

Monotherapy period. A significantly improved efficacy was observed with LEN compared with placebo (87.5% vs. 16.7%, respectively; p<0.0001), with the same treatment difference reported when baseline HIV-1 RNA was adjusted using rank analysis of covariance.

6.17 In the resubmission, CAPELLA data up to week 104 for secondary outcomes from the open label single arm phase (compared to week 52 in the previous submission) was reported (Table 5 and Figure 1).

Table 5: Key secondary efficacy outcomes (Week 52, Week 104; FAS)

Outcome	Time-point	Cohort 1A LEN + OBR (N=24)	Cohort 1B Placebo to LEN + OBR (N=12)	Cohort 1 (1A & 1B) All LEN + OBR (N=36)	Cohort 2 LEN + OBR (N=36)	Cohort 1 & 2 combined LEN + OBR (N=72)
Viral load						
Patients with viral load < 50 copies/mL: US FDA-defined snapshot method, n (n/N at Week 104[a] (%); (95% CI)	Wk 52	21 (87.5) (67.6, 97.3)	9 (75.0) (42.8, 94.5)	30 (83.3) (67.2, 93.6)	26 (72.2) (54.8, 85.8)	**56 (77.8) (66.4, 86.7)**
	Wk 104	17/24 (70.8) (48.9, 87.4)	7/11 (63.6) (30.8, 89.1)	24/35 (68.6) (50.7, 83.1)	20/36 (55.6) (38.1, 72.1)	44/71 (62.0) (49.7, 73.2)
Patients with viral load < 50 copies/mL: Missing = failure, n (%) (n/N at Week 104[a]); 95% CI not reported.	Wk 52	21 (87.5)	9 (75.0)	30 (83.3)	27 (75.0)	57 (79.2)
	Wk 104	17/24 (70.8)	7/11 (63.6)	24/35 (68.6)	20/36 (55.6)	44/71 (62.0)
Patients with viral load < 200 copies/mL: FDA snapshot method, n (%) (n/N at Week 104[a]); (95% CI)	Wk 52	22 (91.7) (73.0, 99.0)	9 (75.0) (42.8, 94.5)	31 (86.1) (70.5, 95.3)	28 (77.8) (60.8, 89.9)	59 (81.9) (71.1, 90.0)
	Wk 104	17/24 (70.8) (48.9, 87.4)	7/11 (63.6) (30.8, 89.1)	24/35 (68.6) (50.7, 83.1)	21/36 (58.3) (40.8, 74.5)	45/71 (63.4) (51.1, 74.5)
Patients with viral load < 200 copies/mL: Missing = failure, n (%), (n/N at Week 104[a]) 95% CI not reported.	Wk 52	22 (91.7)	9 (75.0)	31 (86.1)	29 (80.6)	60 (83.3)
	Wk 104	17/24 (70.8)	7/11 (63.6)	24/35 (68.6)	21/36 (58.3)	45/71 (63.4)
CD4 cell counts – change from baseline						
Baseline CD4 cell count (cells/mm^3)	BL	N=24 199 (166.1) (129, 269)	N=12 99 (115.9) (25, 173)	N=36 166 (157.0) (113, 219)	N=36 258 (273.4) (165, 350)	N=72 212 (226.2) (159, 265)
Mean (SD) change from baseline in CD4 cell count (cells/ mm^3) (95% CI)	Wk 52	N=23 75 (129.6) (19, 131)	N=12 97 (84.6) (43, 150)	N=35 82 (115.3) (43, 122)	N=31 113 (117.9) (70, 156)	N=66 97 (116.7) (68, 125)
	Wk 104	N=20 102 (160.2) (27, 177)	N=10 126 (169.7) (4, 247)	N=30 110 (160.9) (50, 170)	N=25 137 (156.1) (73, 202)	N=55 122 (157.8) (80, 165)

Source: Table 2-20, p101-102 of the resubmission.

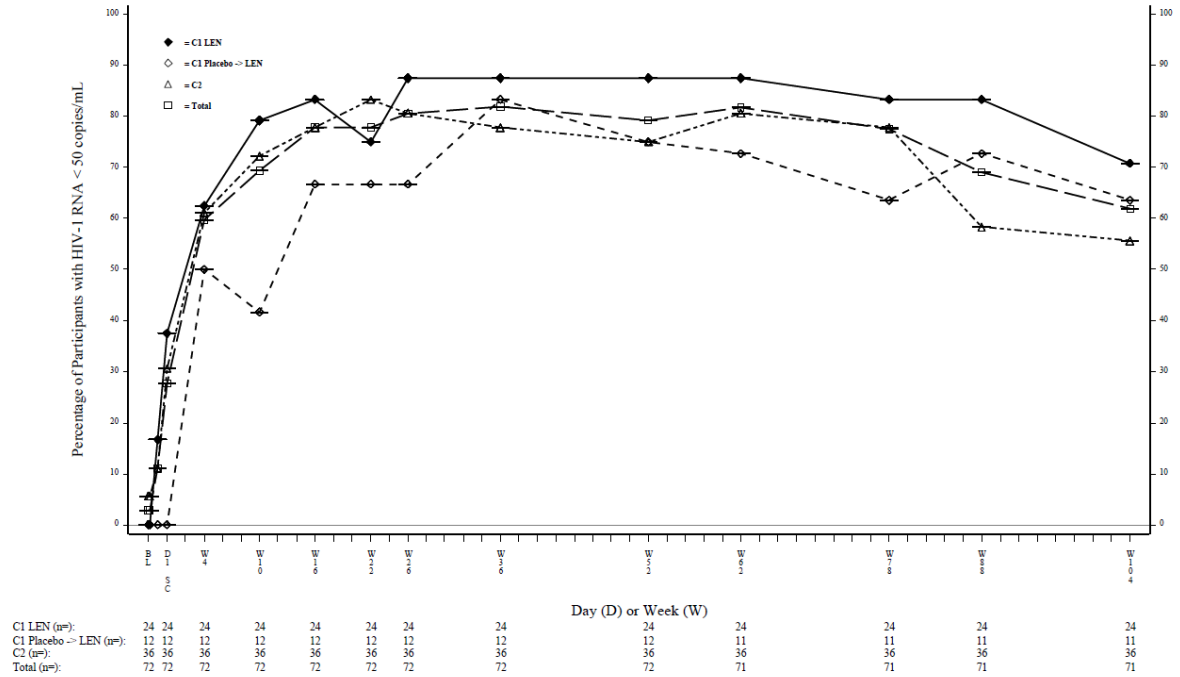
Blue shaded cells represent data previously considered by the PBAC

Values in bold indicate result used in base case of indirect comparison.

BL = baseline; CI = confidence interval; FDA = Food and Drug Administration; LEN = lenacapavir; OBR = optimised background regimen; SD = standard deviation; Wk = week

a At Week 104 there were N=35 patients in Cohort 1 and N=71 patients in combined Cohort 1 & 2. The denominator for percentages at Week 104 is based on the number of participants in the Full Analysis Set for the All LEN analysis, excluding ongoing participants who have missing viral load outcomes at a visit and have not reached the upper limit of the analysis window for the corresponding visit and participants who have missing viral load outcomes at a visit and have completed the study before reaching the upper limit of the analysis window for the visit. Hence 1 patient was missing from the total N, as they had not reached the pre-specified analysis.

Figure 1: Proportion of participants with HIV-1 RNA < 50 copies/mL by visit (missing=failure) up to Week 104



Source: Figure 2-4, p107 of the resubmission.

6.18 Undetectable viral load (< 50 copies/mL) using the missing = failure method was achieved at Week 52 by 83% of patients in the randomised Cohort 1 and 79% in the combined Cohort 1 and Cohort 2 population for those treated with LEN + OBR. The resubmission considered that the high rates of viral load undetectability are supported by increases from baseline in CD4 cell counts observed across all the cohorts. Ongoing maintenance of undetectable viral load was also reported by the majority of patients at Year 2/Week 104, with 69% of Cohort 1 sustaining undetectable viral load < 50 copies/mL.

6.19 The resubmission claimed that between Week 52 and Week 104, all patients in CAPELLA received an oral bridging dose of LEN instead of the subcutaneous (SC) injection that was due at either the Week 52 or Week 78 timepoint. This was because of manufacturing issues with the LEN injection vial which has since been resolved. The resubmission stated that following a review of patients who had achieved undetectable viral load (< 50 copies/mL), a noticeable trend of virologic failure for some patients (5/11 patients; 46% in the randomised Cohort [i.e., Cohort 1]) occurred only after the initiation of oral bridging which was implemented beyond Week 52. While the use of oral bridging at weeks 52 and 78 did not affect the ITC results as only data up to 52 weeks was used, it may provide an indication of what could be expected in the event of missed or delayed SC injections in clinical practice. The evaluation considered that given that oral bridging LEN appears to be less effective than SC LEN (i.e. 46% experience virological failure when switching from SC to oral after week 52, compared to 22.2% of patients who did not achieve <50 copies/mL at 52 weeks using

SC LEN), this raises potential concerns for management of missed SC doses in clinical practice.

6.20 The resubmission also presented a number of post-hoc subgroup analyses of CAPELLA, which, it argued, demonstrated that there was no difference in viral suppression when comparing hMDR HIV patients who used newer ARVs in OBR compared to those who did not. The evaluation considered that given the total sample size of CAPELLA was 72, the lack of significant difference in these analyses were likely driven by the small sample size and may not be informative. For example, 18/22 (81.8%) patients who had IBA or FTR achieved HIV RNA < 50 copies/mL at week 52 compared to 38/50 (76.0%) patients who had neither, however due to small sample sizes, this analysis may not be informative or reliable.

6.21 The resubmission further argued that based on subgroup results in CAPELLA cohort 1, in which 4/6 (67%) patients with no active ARV in OBR and 26/30 (86%) patients with one or more active ARV in OBR achieved undetectable viral load at Week 52, there was a 15-20% difference in proportion of patients achieving viral load suppression based on no or one or more fully active agents in their OBR, and that this reflects the efficacy solely attributable to OBR. The evaluation considered that this conclusion was not reasonable and not supported when considering the results of CAPELLA Cohort 1 and 2 combined. Viral suppression at 104 weeks in CAPELLA was higher in patients with no fully active ARVs in OBR (9/12, 75%) than those with one (17/25, 68%) or two (9/20, 45%) fully active ARVs, which was the opposite to what the resubmission proposed and would be contrary to the expected direction of effect. This may be a reflection on the small sample size in CAPELLA, and as such, any subgroup results from CAPELLA should be considered highly uncertain with results likely due to random variation in individual response.

6.22 To conduct the ITC against OBR, the resubmission meta-analysed the results from the nominated arms of the comparator trials (OBR/comparator arms of BENCHMRK 1 and 2, MOTIVATE 1 and 2 and VICTOR-E with the intervention arms from BRIGHTE and TMB-301). Table 6 presents the results of the proportion of patients with viral load < 50 copies/mL in the individual arms of the studies and trials included to represent OBR alone in the meta-analysis.

Table 6: Patients with a viral load < 50 copies per mL at week 48 in comparator trials

Study ID	n	N	% viral load < 50 copies per mL
BENCHMRK 1	31.4% = 37[a]	118	31.4
BENCHMRK 2	34.5% = 41[a]	119	34.5
MOTIVATE 1	19	118	16.1
MOTIVATE 2	16	91	17.6
VICTOR-E	5	35	14.3
BRIGHTE [b] (FTR+OBR)	184	371	49.6
TMB-301 [c] (IBA+OBR)	17	40	42.5

FTR = fostemsavir; IBA = ibalizumab

Blue shaded cells represent data previously considered by the PBAC

Source: Table 2-28, p115 of the resubmission.

a. Calculated from the reported percentages.
b. Reports viral load <40 copies/mL, assumed to be same as <5F0 copies/mL
c. Reported at Week 25 as this was the study endpoint. As the extension study did not include all patients who were in study TMB-301 data from that study does not provide longer term results for the full study cohort. Both CAPELLA and BRIGHTE (which both investigated newer agents added to OBR in a consistent study design) had very similar results at Week 24/26 and Week 48/52, supporting extrapolation of the Week 25 results in TMB-301 to Week 48/52.

6.23 The resubmission noted that in the November 2022 PBAC submission, all data in the comparator arm of the ITC were from patients randomised to placebo + OBR. In the resubmission, data from the BRIGHTE and TMB-301 were taken from patients treated with a new active agent in combination with OBR (i.e., FTR and IBA, respectively). The resubmission did not adequately address why the placebo + OBR arm for BENCHMRK 1 and 2, MOTIVATE 1 and 2 and VICTOR-E were used to inform the OBR efficacy but the intervention + OBR arm for BRIGHTE and TMB-301 were considered reasonable sources to inform the efficacy of OBR.

6.24 Table 7 presents the results of the resubmission meta-analysis of OBR alone studies/trials. The resubmission noted variability between the results of included studies across the OBR (± placebo) analyses with the undetectable viral load outcome. The PSCR stated a random effects approach was used on the basis of it being standard, and preferred over a fixed effects approach due to the evidence of substantial heterogeneity.

Table 7: Meta-analyses of OBR (± placebo) arms for viral load outcomes at Week 48 (patients reporting viral load <50 copies/mL)

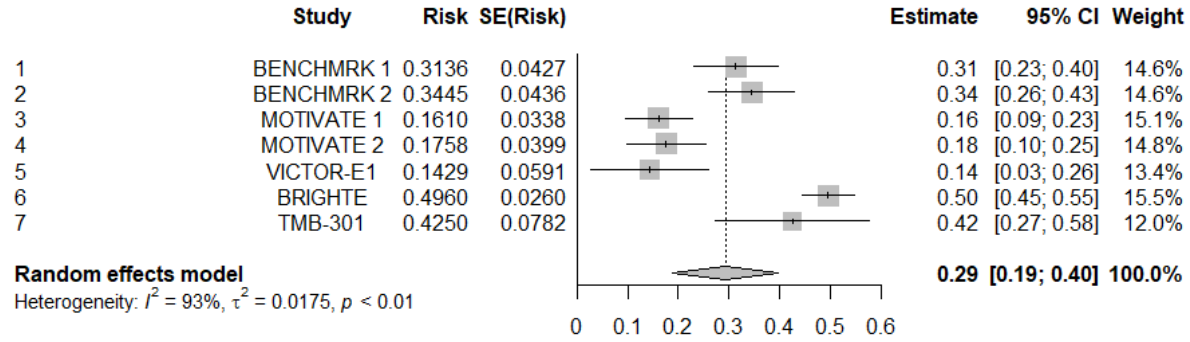
Measure	Estimate	95% CI	Test of heterogeneity	I^2 [95% CI]
Risk	0.2933	0.1892, 0.3974	Q(df=6) = 92.18, P < 0.0001	93.5% [89.0%; 96.1%]
log(Risk)	-1.2659	-1.6225, -0.9093	Q(df=6) = 59.21, P < 0.0001	89.9% [81.7%; 94.4%]
log(Odds)	-0.9138	-1.4280, -0.3996	Q(df=6) = 67.32, P < 0.0001	91.1% [84.2%; 95.0%]
Odds	0.4010	0.2398, 0.6706	-	

Source: Table 2-31, p124 of the resubmission.

CI = confidence interval; OBR =optimised background regimen

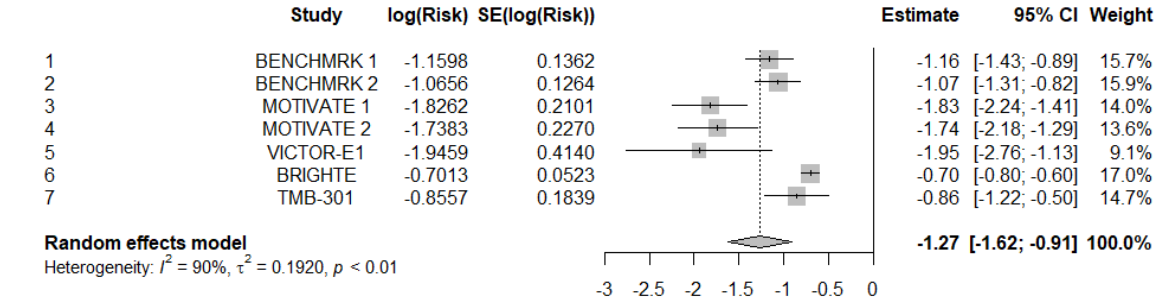
6.25 Figure 2 to Figure 4 present the results of the meta-analysis of OBR alone.

Figure 2: Meta-analysis of patients with viral load < 50 copies/mL: Risk (Week 48)



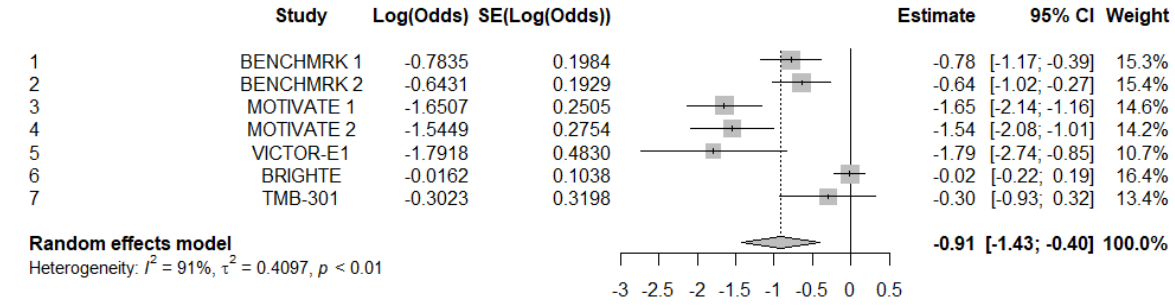
Source: Figure 2-5, p116 of the resubmission.
CI = confidence interval; SE = standard error

Figure 3: Meta-analysis of patients with viral load < 50 copies/mL: log(Risk) (Week 48)



Source: Figure 2-7, p124 of the resubmission
CI = confidence interval; SE = standard error

Figure 4: Meta-analysis of patients with viral load < 50 copies/mL: log(Odds) (Week 48)



Source: Figure 2-8, p125 of the resubmission
CI = confidence interval; SE = standard error

6.26 The meta-analysis of the proportion of patients achieving virologic undetectability (i.e., 'patients with viral load < 50 copies/mL') for the comparator study arm OBR (± placebo) had an overall risk of 0.293 (95% CI 0.189, 0.397).

6.27 Comparatively, the resubmission's survey of 10 Australian clinicians estimated that 49.9% of hMDR-HIV patients on OBR in Australia would achieve and maintain

undetectable viral load < 50 copies/mL (Attachment 1 to the resubmission, Slides 8 and 42), which increased to 62.3% with the introduction of a second generation INSTI (Attachment 1 to the resubmission, Slide 45). These estimates were substantially higher than the estimated viral suppression rate (29.3%) in the resubmission's meta-analysis for OBR alone. This suggests that the resubmission may have substantially underestimated the efficacy of OBR in the Australian setting.

6.28 During the evaluation of the previous submission, it was suggested that it may be more reasonable to use the results of the raltegravir + OBR and maraviroc + OBR arms to inform the efficacy of the comparator instead of the placebo + OBR arms of BENCHMRK 1 & 2 and MOTIVATE 1 & 2. This resulted in an estimate of patients with < 50 copies of HIV RNA/mL at 48 weeks of 56%, which was similar to the Australian clinician estimates.

6.29 The PSCR of the previous submission argued that it was highly inappropriate to include the intervention arms of these trials as the patient populations were specifically naïve to the classes of therapies being investigated in those studies (paragraph 6.33, lenacapavir PSD, November 2022 PBAC meeting). However, as discussed in paragraph 6.23, the current resubmission proposed that the inclusion of data from the intervention + OBR arms of BRIGHTE and TMB-301 was appropriate, which appears to be a change in position from the PSCR for the previous submission.

6.30 The ESC previously acknowledged that the intervention arms of the BENCHMRK and MOTIVATE studies would likely bias in favour of OBR in the comparison as patients in those intervention arms would be expected to perform better where they are specifically receiving a therapy in a new pharmacological class and acknowledged this would likely not be reflective of the target population for LEN, given these patients would have tried and failed almost all available options. However, the ESC also considered it was important that the therapies included in the OBR arm were reflective of contemporary Australian clinical practice (paragraph 6.34, lenacapavir PSD, November 2022 PBAC meeting). The PSCR reiterated that the inclusion of the intervention arms of older trials such as MOTIVATE, BENCHMRK and VICTOR-E would not be appropriate as they do not reflect contemporary ARV options nor clinical practice, and do not include the appropriate patient population that are naïve to the ARV class being investigated. However, the inclusion of FTR and IBA, which are not PBS listed and were not reported to be used by any of the 10 clinicians surveyed by the sponsor, contradicts previous advice from the ESC and the PBAC.

6.31 The resubmission presented a OBR composition analysis whereby the comparison of the proportional ARV classes in OBR between the CAPELLA trial and meta-analysed OBR comparator (weighted by sample size), and argued that the proportion of INSTI, FTR and IBA use was balanced between LEN + OBR and OBR alone. In this analysis, the resubmission grouped second generation INSTIs (e.g. dolutegravir) with first generation INSTIs (raltegravir) even though they may not necessarily have the same impact on response.

6.32 The resubmission did not explain why a 'balancing' of INSTI, FTR and IBA would be a methodologically rigorous way of addressing baseline differences in OBR, especially as the meta-analysis was not weighted by number of patients using each ARV but based on a constructed standard error. A more conventional and rigorous method of adjustment would be the use of a Matching-adjusted indirect comparison (MAIC). However, a MAIC would likely not be reliable given the small sample size of CAPELLA trial. The PSCR stated that it was not possible to remove patients who were treated with FTR or IBA as part of LEN + OBR in the CAPELLA trial nor conduct a MAIC as individual patient level data is not available to the sponsor. The PSCR also agreed that a MAIC would likely not be reliable given the small size of the CAPELLA trial and argued the inclusion of FTR and IBA use in the OBR arm of the ITC to a level consistent with the LEN + OBR arm was the best available approach to balance the use of these agents in both arms of the ITC.

6.33 During the evaluation a comparison of different methods of weighting were explored. This is presented in Table 8.

Table 8: Comparisons of trial weight by analysis

Trial/ study	Weighting		
	Random effects weight (weighting used in the meta-analysis of the resubmission)	Common (fixed) effects weight	Weighting used in OBR composition analysis (weighting by sample size)
BENCHMRK1	14.60%	12.20%	13.20%
BENCHMRK2	14.60%	11.70%	13.30%
MOTIVATE1	15.10%	19.40%	13.20%
MOTIVATE2	14.80%	13.90%	10.20%
VICTOR-E1	13.40%	6.30%	3.90%
BRIGHTE	15.50%	32.90%	41.60%
TMB-301	12.00%	3.60%	4.50%
Meta-analysis/pooled proportion of viral load < 50 copies/mL at 48 weeks	29.30%	32.2%	35.74%

Source: calculated from table 2-33, p128 of the resubmission, and the evaluation replication of the resubmission meta-analysis using the meta package in R (command metagen).
OBR = optimised background regimen

6.34 The weighting used in the meta-analysis differed to the weights used to justify the usage of INSTI, FTR and IBA in the OBR composition analysis presented by the resubmission. Consequently, it is possible that differences in OBR composition remain unaccounted for in the resubmission. For example, the BRIGHTE trial arm, which had the highest treatment effect, received a 15.5% weighting using the random effects model compared to 32.9% in the common effects model and 41.6% in the resubmission OBR composition analysis.

6.35 The weighting has an important impact on the pooled result of effect in the meta-analysed OBR arm. The common (fixed) effects model, for example, estimated the proportion of undetectable HIV-RNA at 32.2% compared to 29.3% in the random effects model and using the sample size as weights (which would be consistent with the 'balancing' of INSTI, IBA and FTR in OBR proposed by the submission) estimated a

value of 35.7% achieving undetectable HIV-RNA in OBR alone. While in theory, a random effects model would be better suited for a meta-analysis with substantial study heterogeneity (as is the case in the resubmission), considering that the random effects model does not necessarily address OBR composition, and there are large differences in the weightings by method, which have a substantial impact on the resulting meta-analysed estimate, a more conservative common effects model could potentially be more pragmatic.

6.36 The ESC considered, given the variability in the weighting results based on the methods used, that the approaches are likely not interchangeable and considered the weights based on variance were likely sub-optimal in this case. The ESC considered given the binomial nature of the data, weights based on sample size may be more appropriate for the meta-analyses of OBR (RR = 2.218; Table 9). The Pre-PBAC Response argued pooling of baseline OBR weights based on sample size was performed to provide an indication of whether the use of INSTIs and new agents was reasonably balanced across LEN + OBR vs. OBR arms only and was not proposed as a means to calculate the relative effectiveness of OBR treatments. Further, the Response noted the advice from the Melbourne Statistical Consulting Centre was that the binomial distribution, sample proportions near zero or one have a smaller variance than those closer to 0.5; therefore the standard approach in pooling sample proportions uses weights related to the variance estimates for statistical optimality reasons. The PBAC considered the advice was informative; however also noted the apparent differences depending on the method used led to uncertainty in estimating the effectiveness of OBR.

6.37 It is important to note that this discussion relates solely to the extent that ARV classes are appropriately balanced between the weighted meta-analysis and the CAPELLA trial. None of these weightings necessarily reflect what would be expected in the Australian treatment setting, which remains uncertain.

6.38 Overall, it was likely that the proportion of patients achieving HIV-1 RNA < 50 copies/mL in OBR alone was underestimated by the resubmission as:

- The weighting used in the base case to pool all nominated OBR arms was the least favourable and was not consistent with the claimed usage of FTR and IBA. Using alternative weighting methods provided OBR estimates of 32.2% to 35.7%;
- The resubmission continued to use the placebo + OBR arms of BENCHMRK, MOTIVATE and VICTOR-E to inform the efficacy of OBR alone, despite accepting that the intervention + OBR results for BRIGHTE and TMB-301 should be used. During the evaluation of the previous submission, using the results of the raltegravir + OBR and maraviroc + OBR arms to inform the efficacy of the comparator instead of the placebo + OBR arms of BENCHMRK 1 & 2 and MOTIVATE 1 & 2 resulted in an estimate of patients with < 50 copies of HIV RNA/mL at 48 weeks of 56%;

- The use of 25-week data from TMB-301 (43% response) as a proxy for week 48 data may have biased against IBA as available week 48 data in the 27/40 patients for whom data is available suggest a higher response rate (67%) at week 48 was possible; and
- The estimate of the proportion of patients who will have HIV-1 RNA < 50 copies/mL in patients treated with OBR alone estimated by the resubmission (29.3%) was substantially lower than estimates provided by 10 Australian clinicians (49.9%, and 62.3% with the inclusion of a second generation INSTI) surveyed by the sponsor.

6.39 The results for the key outcome (patients with viral load < 50 copies per mL at week 48/52) for the ITC are presented in Table 9. Additionally, sensitivity analyses using alternative estimates of OBR efficacy were conducted during the evaluation.

Table 9: ITC Analysis: Comparisons of LEN + OBR with OBR (± placebo): Patients with viral load < 50 copies/mL at Week 48 or 52

CAPELLA population	Estimate or meta-estimate		LEN + OBR vs. OBR alone		
	LEN + OBR	OBR alone	Estimate	95% CI	P-value
	Risk	**Risk**	**Risk difference***		
Combined Cohort 1 & 2	0.792	0.293	0.498	0.358, 0.638	<0.001
Cohort 1	0.833	0.293	0.540	0.380, 0.700	<0.001
			Relative risk*		
Combined Cohort 1 & 2	0.792	0.282	2.807	1.928, 4.088	<0.001
Cohort 1	0.833	0.282	2.955	2.01, 4.345	<0.001
	Odds	**Odds**	**Odds ratio***		
Combined Cohort 1 & 2	3.800	0.401	9.476	4.402, 20.400	<0.001
Cohort 1	5.000	0.401	12.469	4.513, 34.449	<0.001
Evaluator indicative analysis using clinical expert estimate of OBR efficacy					
			Risk difference*		
Combined Cohort 1 & 2	0.792	0.499	0.293	NC	
Cohort 1	0.833	0.499	0.334		
			Relative risk*		
Combined Cohort 1 & 2	0.792	0.499	1.587	NC	
Cohort 1	0.833	0.499	1.669		
Evaluator indicative analysis using clinical expert estimate of OBR efficacy (62.3% 2nd generation INSTIs)					
			Risk difference*		
Combined Cohort 1 & 2	0.792	0.623	0.169	NC	
Cohort 1	0.833	0.623	0.21		
			Relative risk*		
Combined Cohort 1 & 2	0.792	0.623	1.271	NC	
Cohort 1	0.833	0.623	1.337		
Evaluator indicative analysis using weighting by trial population size					
			Risk difference*		
Combined Cohort 1 & 2	0.792	0.357	0.435	NC	
Cohort 1	0.833	0.357	0.476		
			Relative risk*		
Combined Cohort 1 & 2 ***(ESC preferred)***	0.792	0.357	**2.218**	NC	
Cohort 1	0.833	0.357	2.333		
Evaluator indicative analysis using fixed effects model					
			Risk difference*		
Combined Cohort 1 & 2	0.792	0.322	0.47	NC	
Cohort 1	0.833	0.322	0.511		
			Relative risk*		
Combined Cohort1 & 2	0.792	0.322	2.460	NC	
Cohort 1	0.833	0.322	2.587		

Blue shaded cells represent results previously considered by the PBAC.
Source: Table 2-32, p125 of the resubmission.
LEN = lenacapavir; NC = not calculable; OBR = optimised background regimen;
Missing=failure viral load <50 copies/mL outcomes utilised for CAPELLA. 'Snapshot' outcomes for CAPELLA were also analysed in the ITC Report in Attachment 4 of the resubmission.
*Higher values of risk difference, relative risk and odds ratio favour LEN.

6.40 The resubmission used a risk estimate based on the result of the exponential of the Log(risk) meta-analysis ($0.282 = e^{-1.27}$, see Table 7) rather than the actual risk estimate (0.293) to estimate the relative risk (RR), with the difference in magnitude likely

attributable to different weights being used for the comparator studies (see Figure 2 and Figure 3). It was unclear if this approach was appropriate, or if the 0.293 result from the risk estimate should have been used. The use of 0.282 as the risk estimate for OBR alone to calculate the RR (which is used in the economic model) favoured LEN + OBR.

6.41 In the previous submission a RR of viral suppression of 3.828 (95% CI: 2.592, 5.655) based on the results from CAPELLA Cohort 1A was estimated and used in the base case of the economic model. Comparatively, the RR of 2.807 (95% CI: 1.928, 4.088) nominated as the base case (based on combined CAPELLA Cohort 1 & 2) in the resubmission represented a 27% decrease in the point estimate.

6.42 Using alternative methods of weighting to derive OBR viral suppression or estimates for OBR viral suppression based on Australian clinicians surveyed by the resubmission resulted in risk difference estimates ranging from 0.169 to 0.47 and relative risk estimates ranging from 1.271 to 2.460 (combined Cohort 1 and 2). The evaluation considered this suggested that the base case presented in the resubmission was likely optimistic and favoured LEN + OBR.

6.43 The PSCR argued the clinical survey was never intended, nor powered, to inform quantitative outcomes and it was unreasonable to consider survey outcomes to provide meaningful estimates given the small number of participants. Rather, the PSCR argued the survey did clearly establish the clinical need for treatments for hMDR people living with HIV.

6.44 The ESC considered an assumption that OBR was likely more effective in contemporary Australian practice than estimated in the submission may be reasonable, and the advice from surveyed clinicians may reflect the public health successes of Australia's response to HIV over several decades. While using the clinician survey as the basis for the effectiveness estimates was not the preferred approach, the ESC considered the survey did highlight that some hMDR patients are effectively managed in Australia with current treatment regimens. The PBAC concurred with the ESC and considered that whilst the results of the clinician survey were not an appropriate basis for determining an estimate of the effectiveness of OBR for use in the clinical comparison, did consider the survey highlighted the broad view that a substantial proportion of Australian patients who would be considered hMDR are adequately managed on individualised anti-retroviral therapy regimens.

Comparative harms

6.45 Safety outcomes from CAPELLA for up to 104 weeks was presented in the resubmission. While point estimates of adverse events (AEs) were slightly higher at Week 104 compared to Week 52 (presented in the previous submission), this was consistent with a longer follow-up. Overall, no new safety signals were identified from the Week 104 data from CAPELLA.

6.46 In the 14-day randomised period of CAPELLA, notably more patients treated with LEN + failing ARV regimen experienced AEs (9/24, 37.5%) than patients treated with placebo + failing ARV regiment (3/12, 25%). This was also observed for treatment emergent adverse events (TEAEs) of grade 2 or higher (3/24, 12.5% compared to 0/12, 0%). No deaths were reported during the 14-day randomised period.

6.47 The resubmission presented a naïve comparison of safety outcomes in CAPELLA (at 52 weeks) and the comparator trials. This is presented in Table 10. The resubmission considered that, overall, the rate of reporting of TEAEs, TEAEs leading to discontinuation and specific TEAEs was comparable across the CAPELLA and comparator studies.

6.48 In November 2022, the PBAC had considered that while LEN was associated with increased injection site reactions and nausea compared to OBR, the submission's claim of non-inferior safety was overall likely to be reasonable. However, the Committee considered this claim remained somewhat uncertain due to the small sample size of CAPELLA and the absence of long-term safety data (paragraph 7.7, lenacapavir PSD, November 2022 PBAC meeting). Overall, the ESC considered the naïve comparison of safety outcomes out to Week 104 was consistent with this previous conclusion.

Table 10: TEAEs reported in the OBR (± Placebo) arm in comparator studies (varying reporting durations)

	Reported in November 2022 Submission					Data added in this resubmission	
	CAPELLA Cohort 1	CAPELLA Cohort 1&2 combined	BENCHMRK 1 & 2	MOTIVATE 1 & 2	VICTOR-E1	BRIGHTE	TMB-301
	LEN + OBR (N=36)	LEN + OBR (N=72)	Placebo + OBR (N=237)	Placebo + OBR (N=209)	Placebo + OBR (N=35)	FTR + OBR (N=371)	IBA + OBR (N=40)
Reporting duration	52 weeks	52 weeks	48 weeks	48 weeks	48 weeks	48 weeks or 96 weeks	25 weeks
Any TEAE, n (%)	34 (94)	69 (96)	209 (88)	177 (85)	33 (94)	343 (92)	32 (80)
Treatment-related TEAE, n (%)	23 (64)	50 (69)	131 (55)	94 (45)	NR	290 (78) (Grade 2-4 only)	7 (18)
TEAEs, severe (Grade 3, 4), n (%)	7 (19)	19 (26)	NR	NR	7 (20)	117 (32)	11 (28)
TEAEs, serious, n (%)	6 (17)	10 (14)	45 (19.0)	60 (28.7)	NR	129 (35)	9 (23)
TEAE leading to discontinuation, n (%)	1 (3)	3 (4)	7 (3)	6 (3)	NR	27 (7)	5 (13)
Deaths, n (%)	0	2 (3)	6 (3)	2 (1)	2 (6)	25 (7)	4 (40)
Any TEAE occurring in ≥10% of patients in any treatment arm, n (%)							
Diarrhoea	6 (17)	10 (14)	50 (21)	50 (24)	9 (26)	83 (22)	8 (20)
Nausea	7 (19)	10 (14)	34 (14)	42 (20)	5 (14)	60 (16)	5 (13)
Vomiting	1 (3)	4 (6)	22 (9)	23 (11)	3 (9)	38 (10)	4 (10)
Constipation	6 (17)	9 (13)	1 (0.4)	6 (3)	NR	NR	NR
Flatulence	1 (3)	1 (1)	7 (3)	7 (3)	4 (11)	NR	NR
Abdominal distention	5 (14)	7 (10)	7 (3)	NR	NR	NR	NR
Arthralgia	4 (11)	6 (8)	7 (3)	3 (3)	2 (6)	NR	NR
Rash	2 (6)	6 (8)	NR	11 (5)	NR	11/370 (3)	5 (13)
Headache	2 (6)	7 (10)	30 (13)	36 (17)	7 (20)	46 (12)	3 (8)
Dizziness	3 (8)	5 (7)	6 (3)	17 (8)	4 (11)	23/370 (7)	5 (13)
Fatigue	4 (11)	5 (7)	11 (5)	35 (17)	3 (9)	22/370 (6)	NR
Depression	1 (3)	0 (0)	9 (4)	8 (4)	6 (17)	NR	NR
Pyrexia	3 (8)	8 (11)	30 (13)	25 (12)	4 (11)	41 (11)	5 (13)
Cough	6 (17)	8 (11)	8 (3)	13 (6)	2 (6)	43 (12)	NR
Nasopharyngitis	1 (3)	3 (4)	14 (6)	13 (6)	2 (6)	43 (12)	4 (10)
Upper respiratory tract infection	1 (3)	2 (3)	17 (7)	15 (7)	3 (9)	50 (13)	3 (8)
Lymphadenopathy	2 (6)	2 (3)	7 (3)	1 (0.5)	2 (6)	NR	4 (10)
Sinusitis	0	1 (1)	8 (3)	5 (2)	2 (6)	36/370 (10)	NR
COVID-19	4 (11)	9 (13)	NA	NA	NA	NA	NA
Injection site reactions							
Injection site swelling	14 (39)	28 (38.9)	NR	NR	NR	NR	NR
Injection site pain	14 (39)	27 (37.5)	3 (1)	6 (3)	NR	NR	NR
Injection site erythema	10 (28)	24 (33.3)	NR	NR	NR	NR	NR
Injection site nodule	14 (39)	20 (27.8)	NR	NR	NR	NR	NR
Injection site induration	2 (6)	11 (15.3)	NR	NR	NR	NR	NR

Source: Table 2-38, pp135-136 of the resubmission.
Blue shaded cells represent results previously considered by the PBAC.
AE = adverse events; NR: not reported; TEAE: treatment-emergent adverse event.
TEAEs occurring during the 48-week study treatment periods are reported. Median duration of actual treatment in the studies will vary.
* AEs reported up to Week 96 in clinical study report (ViiV Healthcare 2015) Kozal 2020 reports AEs in ≥10 patients at Week 52 only

Benefits/harms

6.49 A summary of the comparative benefit and harms of LEN + failing therapy and placebo + failing therapy is presented in Table 11. These were based on the 14-day randomised period of the CAPELLA trial. This has not changed since the previous submission.

Table 11: Summary of comparative benefits and harms for lenacapavir + failing regimen versus placebo + failing regimen

Trial	LEN + failing regimen n/N (%)	PBO + failing regimen n/N (%)	Event rate/100 patients per 14 days		Risk difference (95% CI)
			LEN	PBO	
Benefits					
Patients achieving ≥ 0.5 log_{10} copies/mL reduction from baseline in HIV-1 RNA, n (%)					
CAPELLA	21/24 (87.5)	2/12 (16.7)	87.5	16.7	70.8 (34.9, 90.0)
Harms					
Number (%) of patients with AE	9/24 (37.5)	3/12 (25.0)	37.5	25.0	12.5 (-21.46, 40.14)
TEAE of Grade 2 or higher	3/24 (12.5)	0/12 (0)	12.5	0	12.5 (-13.41, 31.32)

Source: Table 2-26, p107 and Table 2-44, p131-132 of the submission.
Blue shaded cells represent results previously considered by the PBAC.
AE = adverse event; CI = confidence interval; HIV = Human immunodeficiency virus; LEN = lenacapavir; mL = millilitre; NR, not reported; PBO = placebo; RNA = ribonucleic acid. TEAE = treatment emergent adverse event

6.50 On the basis of the 14-day randomised period of the CAPELLA trial, for every 100 patients treated with LEN + failing therapy in comparison with placebo + failing therapy:

- Approximately 71 additional patients will achieve ≥ 0.5 log_{10} copies/mL reduction from baseline in HIV-1 RNA.
- Approximately 13 additional patients will experience a treatment emergent adverse event of grade 2 or higher.

6.51 A summary of the comparative benefit of LEN + OBR and OBR alone based on the unanchored indirect comparison was presented in Table 9. Conclusions regarding comparative safety could not be informed by the indirect comparison presented in the submission.

6.52 On the basis of the submission's unanchored indirect comparison of the CAPELLA trial (Cohorts 1 & 2) and meta-analysed results of seven comparator trials presented by the submission, for every 100 patients treated with LEN + OBR in comparison with OBR alone:

- Approximately 50 additional patients will achieve virologic suppression (less than 50 copies of HIV RNA /mL of blood) at 52 weeks.

Clinical claim

6.53 The resubmission claimed that, for PLWH who are hMDR, LEN + OBR is superior in terms of effectiveness compared with OBR (± placebo) or OBR alone. Additionally, LEN + OBR is non-inferior in terms of safety compared with OBR.

6.54 In consideration of the November 2022 submission, the PBAC had considered that the claim of superior comparative effectiveness was uncertain (paragraph 6.62, lenacapavir PSD, November 2022 PBAC meeting). The PBAC previously noted there was uncertainty about the applicability of the evidence to the proposed PBS population, substantial uncertainty in comparator selection and assessing the comparative effectiveness of LEN and inconsistencies and transitivity issues in the ITC including the small patient numbers in CAPELLA, the lack of a common comparator, and differences in the trial populations (e.g. differences in susceptibility of OBR regimen or agents used) (paragraphs 7.5-7.6, lenacapavir PSD, November 2022 PBAC meeting).

6.55 The clinical claim in the resubmission remains uncertain for similar reasons as the previous submission. Although the resubmission has presented an updated ITC analysis which, the resubmission argues, addresses the imbalances in ARV class of OBR, the efficacy of the comparator of OBR alone was likely underestimated as:

- The weighting used in the base case to pool all nominated OBR arms was the least favourable towards OBR alone and was not consistent with the claimed usage of FTR and IBA;
- The use of 25-week data from TMB-301 (43% response) as a proxy for week 48 data may have biased against IBA as available week 48 data in the 27/40 patients for whom data is available suggest a higher response rate (67%) at week 48 was possible; and
- The estimate of proportion of patients who will have HIV-1 RNA < 50 copies/mL in patients treated with OBR alone used in the submission's base case (29.3%) was substantially lower than estimates provided by 10 Australian clinicians (49.9-62.3%) surveyed by the sponsor. Further, using alternative weighting methods provided OBR estimates of 32.2% to 35.7% which were higher than the resubmission's base case (29.3%).

6.56 Consequently, the ITC results provided in the resubmission likely favoured LEN + OBR. Additionally, it was uncertain that the inclusion of FTR and IBA in the OBR alone arm was appropriate given neither ARV is PBS-listed and Australian clinicians surveyed by the sponsor indicate that no patients are treated with either ARV in Australia. Moreover, the resubmission's approach of demonstrating a 'balance' of INSTI, FTR and IBA use between arms to provide certainty that OBR arms of the included comparator studies would reflect treatment efficacy in the Australian setting was poorly justified and was not reflected in the weighting used in the meta-analysis of OBR alone studies.

6.57 Further, while the resubmission provided an ITC based on the combined Cohort 1 and 2 of CAPELLA, and thus provided a larger sample size, the overall sample size of CAPELLA (n=72) remained small, and the ITC remained unanchored. The included trials/studies to inform OBR alone also had substantial heterogeneity. The PSCR argued the use of an unanchored ITC was reasonable in the context of the design of the CAPELLA trial in hMDR people living with HIV, where FDA guidance considered

long term treatment with placebo + OBR to be unethical, therefore no comparator arm was appropriate for the pivotal study.

6.58 Overall, the ESC considered that the results remain highly uncertain, and the estimate of the incremental clinical benefit with LEN + OBR was likely overestimated and favoured LEN + OBR.

6.59 With regards to the non-inferior safety claim, the PBAC had previously considered that that while LEN was associated with increased injection site reactions and nausea compared to OBR, the submission's claim of non-inferior safety was overall likely to be reasonable. However, the Committee considered this claim remained somewhat uncertain due to the small sample size of CAPELLA and the absence of long-term safety data (paragraph 7.7, lenacapavir PSD, November 2022 PBAC meeting).

6.60 Overall, longer 104-week follow-up safety data from CAPELLA indicated no new safety signals associated with LEN + OBR, giving some additional support to a claim of non-inferior safety. However, the small sample size in CAPELLA may limit the ability of rarer safety signals to be detected.

6.61 The PBAC considered that based on the available data, the claim that LEN (in combination with OBR), is of superior comparative effectiveness to OBR alone was supported, in the proposed small population of patients with hMDR HIV infection. However, the PBAC considered the uncertainties in the clinical comparison meant that the magnitude of benefit could not be accurately determined.

6.62 The PBAC noted updated safety data out to week 104 was presented in the resubmission with no new safety signals identified, and reaffirmed its previously expressed view in November 2022 that the claim of non-inferior comparative safety was likely to be reasonable.

Economic analysis

6.63 The ESC considered the economic model presented in the resubmission was unreliable for decision-making. In providing this advice, the ESC considered that there were a number of key issues that resulted in the model producing counter-intuitive and often unrealistic and impossible inputs and outcomes, resulting in the model lacking both face validity and technical operability (see paragraph 6.89).

6.64 The submission presented a cost-utility analysis based on data from the CAPELLA trial and the ITC described above.

6.65 The resubmission model was the same as the previous model with the following key changes:

- Updated requested price of LEN;
- Updated number of oral LEN tablets for initiation from four to five;
- Removed modelling for adherence benefit;

- Updated CAPELLA data from Cohort 1A to Cohorts 1 & 2 and incorporated up to week 104 data;
- Started extrapolation from Week 104 rather than from the first transition (i.e. cycle 1) to inform LEN + OBR viral suppression, using observed data from CAPELLA up to week 104 instead; and
- Updated other costs (OBR, ARE, drug administration, treatment switching) to reflect current prices.

6.66 The overall structure of the economic model was unchanged from the original submission. As in the previous submission, patients transition between health states defined by both viral load and CD4 cell count (for example, such a state may be defined as: viral load < 50 copies/mL, and CD4 cell count > 500 cells/mm^3). Each health state was associated with a specific disease management cost. Patients with CD4 < 200 cells/mm^3 (irrespective of treatment) were assigned probabilities associated with acquired immunodeficiency syndrome (AIDS) related events (AREs) which led to increased disutility and higher costs. Mortality was a function of CD4 cell count and age.

6.67 Table 12 presents a summary of the model structure and key inputs and rationale of the economic evaluation.

Table 12: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	LEN + OBR vs OBR
Time horizon	A life-time time horizon based on 14 days of randomised comparative data and 52 weeks of non-randomised data.
Outcomes	LYG and QALYs
Methods used to generate results	Markov state transition model
Health states	Unchanged from previous submission. States defined by viral load (<50, 50-199, >200) and CD4 cells count (<50, 50-199, 200-499, >500).
Costs	As in the previous submission, the resubmission estimated drug acquisition costs, administration costs, disease management costs, ARE costs, treatment switching costs, and societal costs (not in the base case). Disease management costs included in the model depended on CD4 cell count and were sourced from Schneider (2014), a detailed micro-costing (conducted using 2013 costs) conducted for the Australia setting. The resubmission updated costs and updated the modelling of ARE costs to account for the risk of double counting. Overall, the model was not sensitive to costs outside of drug acquisition costs.
Cycle length	3 months
Transition probabilities	Based on individual patient data from CAPELLA and the literature. Mortality was modelled by CD4 health state based on data from Mangal (2017) and Australian life tables.
Extrapolation method	Virologic suppression at < 50 copies/mL and at < 200 copies/mL were extrapolated using exponential models. No other parametric models were tested. The resubmission's base case used the extrapolated transitions at the end of the available trial data (week 104). This differed from the original submission where the model was extrapolated from the initiation of the model.
Health related quality of life	Unchanged from previous submission. Utility values were sourced from Schneider (2014), based on Tengs (2002). Utility values were based on CD4 count (copies/mm^3): < 50 = 0.702; 50-200 = 0.702; 200-500 = 0.877; > 500 = 0.935

Source: Table 3.1, p144 of the resubmission and Table 11, p26 of the previous Commentary
ARE = AIDS-related costs; LEN = lenacapavir; LYG = life-years gained; OBR = optimised background regimen; TRAE = treatment related adverse events; QALY = quality-adjusted life years

6.68 In consideration of the previous submission the ESC considered that 'due to the small size of the CAPELLA study, there was insufficient data to inform a 16 health state model and therefore the model, as presented, was likely not informative for decision-making. Furthermore, the ESC noted that while longer-term open label data may have been used in the model, only 14 days of randomised data was available and considered this also introduced substantial additional uncertainty to an economic model extrapolated to a lifetime' (paragraph 6.70, lenacapavir PSD, November 2022 PBAC meeting). The PBAC previously agreed with ESC that the model was not informative for decision making (paragraph 7.8, lenacapavir PSD, November 2022 PBAC meeting).

6.69 The resubmission was based on the combined Cohort 1 & 2 of the CAPELLA trial (n=72), compared to 24 patients in Cohort 1a in the previous submission. This was appropriate, although the sample size remained small relative to the number of health states (16).

6.70 In consideration of the previous submission, the ESC noted that 'the submission's base case transition probabilities remain unexplained and favoured lenacapavir' (paragraph 6.74, lenacapavir PSD, November 2022 PBAC meeting). The resubmission probabilities have been verified and are consistent with those reported in the CAPELLA 104-week analysis tables.

6.71 In the previous submission, viral load transitions in the base case were based on an exponential curve fitted to the proportion of individuals with < 50 and < 200 copies/mL of HIV-RNA throughout the entire duration of the model. The resubmission considered that as all 72 patients from CAPELLA were included and given the availability of Week 104 CAPELLA data for this resubmission, observed trial data is used up to Week 104 and thereafter the exponential extrapolation function was used to inform LEN + OBR viral load. Viral load in OBR alone however was completely modelled and no KM data from any of the OBR comparator trials were used directly in the model. Specifically, the OBR arm was modelled by applying the RR of viral load at < 50 copies/mL and < 200 copies/mL sourced from the indirect treatment comparison to the LEN + OBR arm at each cycle.

6.72 The previous submission considered the use of the exponential curve from model initiation, rather than after week 104, was conservative because the alternative approach (using the observed data to week 104) would result in greater viral load suppression in the first two years of the model and therefore decrease the modelled incremental cost-effectiveness ratio (ICER). The PBAC previously considered that this was reasonable (paragraph 6.77, lenacapavir PSD, November 2022 PBAC meeting). The resubmission however revised the approach, and the use of the observed CAPELLA data for up to week 104 favoured LEN and also caused the model to behave in an unexpected manner.

6.73 Firstly, given the substantial decrease in incremental benefit (27%, see paragraph 6.41) relative to the smaller price decrease (%, see paragraph 3.3), a higher ICER compared to the previous submission (previous submission ICER = $75,000 to < $95,000/QALY) was expected, however the resubmission reported a base case ICER which was 16% lower (resubmission base case ICER = $75,000 to < $95,000/QALY). Additionally, there was an unexpected increase in the incremental QALY gain (3.09 QALY gained in the resubmission compared to 1.97 QALY gained in the previous submission) which was inconsistent with the assumption of a lower incremental benefit.

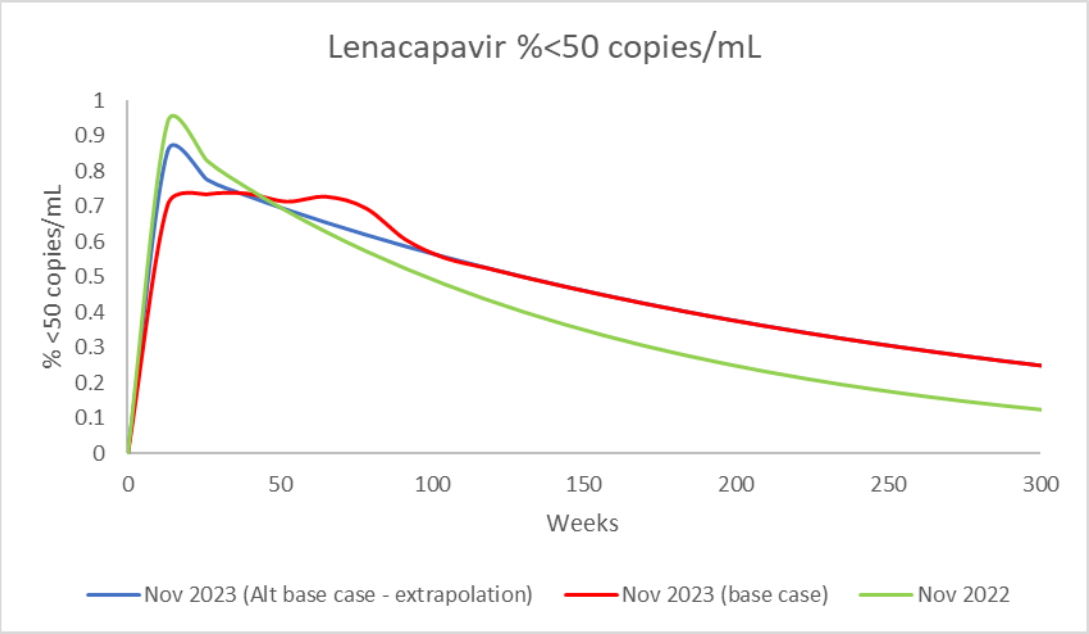
6.74 Secondly, the incorporation of the clinical data from model initiation in the resubmission base case appeared to have created illogical viral load transition probabilities being either greater than 100% or less than 0%.

6.75 Consequently, during the evaluation, an alternative analysis was proposed whereby the exponential curve is used to inform viral load in LEN + OBR from the first model transition (i.e. cycle 1) rather than after week 104 (i.e. cycle 9). This increased the base case ICER to $115,000 to < $135,000/QALY, which is consistent with the decreased

incremental benefit (and small price discount) assumed in the resubmission, relative to the previous submission.

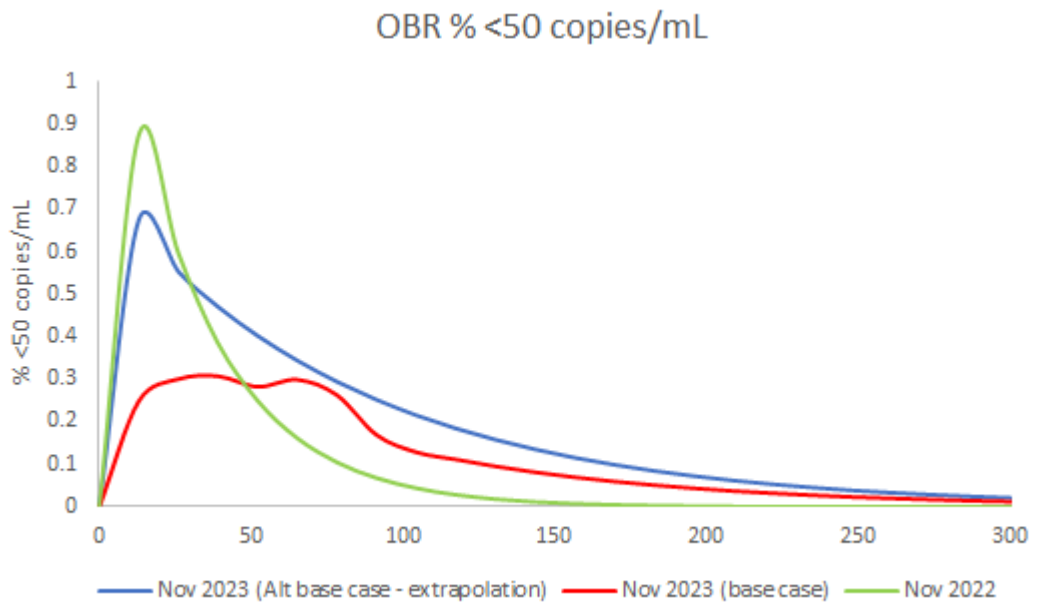
6.76 Figure 5 and Figure 6 present traces of the proportion of patients with < 50 copies/mL for the original submission, the resubmission base case, and the resubmission alternative base case in the LEN and OBR arms. After week 104, the alternative base case and the resubmission base case for LEN have the same values.

Figure 5: Trace of percent of patients with viral load < 50 copies/mL, LEN arm



Source: constructed during the evaluation.
ICER = incremental cost effectiveness ratio; LEN = lenacapavir; Nov = November
ICER in November 2022 was $75,000 to < $95,000; ICER in November 2023 resubmission base case is $75,000 to < $95,000; ICER in November 2023 alternative base case is $115,000 to < $135,000.

Figure 6: Trace of percent of patients with viral load< 50 copies/mL, OBR arm



Source: Constructed during the evaluation
ICER = incremental cost-effectiveness ratio; Nov = November; OBR = optimised background regimen
ICER in November 2022 was $75,000 to < $95,000; ICER in November 2023 resubmission base case is $75,000 to < $95,000; ICER in November 2023 alternative base case is $115,000 to < $135,000.

6.77 The traces show that using modelled data to inform the LEN + OBR values up to Week 104 (as opposed to observed data from CAPELLA) had only a moderate effect on modelled effect the LEN arm up to week 104, after which there was no difference between methods of estimating proportion of patients with < 50 copies/mL in LEN + OBR. However, surprisingly, this had a large impact on the virological response modelled in the OBR arm over the entire model duration. The evaluation considered this relationship did not appear to have face validity and raised concerns about the reliability of the resubmission's model. The PBAC noted the virological response for the OBR arm was higher, and hence more conservative, when the modelled data for LEN was used for the first 104 weeks of the model (Figure 6).

6.78 The alternative base case addresses some of the key operational issues of the economic model of the resubmission. However, even the alternative base case behaved in unexpected ways as, for example, assuming 100% efficacy for LEN + OBR in cycle 1 (i.e. all patients will achieve < 50 copies/mL in cycle 1/week 13, but all else unchanged) paradoxically increased the ICER by 3.5% and delivered a lower QALY gain than the base case, when an improvement in LEN + OBR response would be expected to decrease the ICER and deliver a higher QALY gain. This illustrates that even with the alternative base case (which functioned similarly to the previous model) there were other structural issues and assumptions associated with the model and the economic evaluation results cannot be considered robust.

6.79 As in the previous submission, the transition probabilities for viral load suppression in the OBR arm were based on the LEN arm transition probabilities with a RR from the ITC applied. In the previous submission a RR of viral suppression of 3.828 (95% CI: 2.592, 5.655) had been applied to both the transitions to > 50 copies and > 200 copies of viral RNA / mL. In the resubmission this value was 2.807 (95% CI: 1.928, 4.088). As discussed in paragraphs 6.55 and 6.56, this estimate was likely overestimated due to uncertain estimation of viral suppression in the meta-analysed OBR arm.

6.80 Appropriately, modelling of an adherence benefit was removed from the economic model of the resubmission, which was previously requested by the ESC (paragraph 6.80, lenacapavir PSD, November 2022 PBAC meeting).

6.81 The resubmission relied on the same health state utility estimates as in the previous submission (Schneider 2014) which were based on utility values on from Tengs (2002), a meta-analysis of utility estimates for HIV/AIDS.

6.82 The resubmission model (even with the alternative base case) continued to estimate a substantial mortality benefit from LEN + OBR versus OBR and there was a lack of evidence to support this. The life years gained from treatment with LEN + OBR compared with OBR in the resubmission base case (3.26 years) exceeded that in the previous submission (2.05 years). In the resubmission base case, 50% of patients in the OBR arm had died after 7.25 years (versus 10 years in the previous submission) but it took an additional 12 years (versus an additional 8 years in the previous submission) for the LEN + OBR arm to reach 50% death. The life years gained from treatment with LEN + OBR compared with OBR in the alternative base case (1.93 years) was similar to that in the previous submission (2.05 years).

6.83 Overall, the evaluation considered the economic model may be overly optimistic and the relationship between changing LEN + OBR efficacy and how it impacts OBR alone efficacy may lack face validity, and the model may not be informative for decision making.

6.84 Table 13 and Table 14 present the economic evaluation results in the resubmission base case and the alternative base case using modelled data from cycle 1, respectively.

Table 13: Results of the economic evaluation (resubmission base case)

Component	LEN + OBR	OBR	Increment
Costs ($)	[redacted]	$167,947	[redacted]
LYs	10.85	7.59	3.26
QALYs	9.47	6.37	3.09
Incremental cost/extra QALY gained			[redacted][1]**/QALY**

Source: Table 3-7, p160 of the resubmission.
LEN = lenacapavir; LY = life year; OBR = optimised background regimen; QALY = quality adjusted life year
The redacted values correspond to the following ranges:
[1] $75,000 to < $95,000

Table 14: Results of the economic evaluation (alternative base case)

Component	LEN + OBR	OBR	Increment
Costs ($)	[redacted]	$198,909	[redacted]
LYs	10.92	8.99	1.93
QALYs	9.52	7.65	1.87
Incremental cost/extra QALY gained			[redacted][1] **/QALY**

Source: constructed during the evaluation by applying extrapolation from model initiation in attached economic model.
LEN = lenacapavir; LY = life year; OBR = optimised background regimen; QALY = quality adjusted life year
The redacted values correspond to the following ranges:
[1] $115,000 to < $135,000

6.85 For comparison, the results from the previous submission are presented in Table 15 .

Table 15: Results of the economic evaluation from November 2022

Component	LEN + OBR	OBR	Increment
Costs	[redacted]	$223,839	[redacted]
LYG	10.68	8.63	2.05
QALYs	**9.24**	**7.27**	**1.97**
Incremental cost/extra LYG			[redacted][1]/LYG
Incremental cost/extra QALY gained			[redacted][1]**/QALY**

Blue shaded cells indicate values previously considered by the PBAC
Source: Table 3-27, pp178-179 of the November 2022 submission., LEN CEM – Final 6July22.xlsm
LEN = lenacapavir; LYG = life years gained OBR = optimised background regimen; QALY = quality adjusted life year
The redacted values correspond to the following ranges:
[1] $75,000 to < $95,000

6.86 The alternative base case ICER of $115,000 to < $135,000/QALY represents a 26% increase from the previous submission base case ICER of $75,000 to < $95,000/QALY, which the PBAC had considered to be 'unacceptably high at the proposed price' (paragraph 7.8, lenacapavir PSD, November 2022 PBAC meeting).

6.87 The results of sensitivity analyses for the alternative base case are summarised in Table 16. Due to unreliable nature of the economic model, these analyses should be interpreted with caution.

Table 16: Results of sensitivity analyses using alternative base case

Parameter (base case value)	Sensitivity analysis	Incremental cost	Incremental QALY	ICER	% Change
Alternative base case:			**1.87**	[redacted][1]	-
Time horizon (44 years)	10 years		0.76	[redacted][2]	[redacted]
	20 years		1.48	[redacted][3]	[redacted]
Discount rate (5%)	3.5%		2.29	[redacted][1]	[redacted]
	0%		3.94	[redacted][4]	[redacted]
Efficacy sensitivity analyses					
OBR, relative risk of viral load at both 50 copies/mL and 200 copies/mL (RR 2.81) (see Table 9)	RR=1.587 (based on expert estimate of OBR efficacy)	[redacted]	0.80	[redacted][5]	[redacted]
	RR=1.271 based on clinical expert estimate of 2nd gen INSTI efficacy	[redacted]	0.40	[redacted][6]	[redacted]
	RR = 2.218 (unadjusted trial weights)	[redacted]	1.41	[redacted][3]	[redacted]
	RR = 2.460 (fixed effects model)	[redacted]	1.61	[redacted][1]	[redacted]

Source: Attached economic model Excel worksheet

ICER = incremental cost-effectiveness ratio; LEN = lenacapavir; mL = millilitre OBR = optimised background regimen; QALY = Quality-adjusted life year; RR = relative risk

The redacted values correspond to the following ranges:

[1] *$115,000 to < $135,000*

[2] *$255,000 to < $355,000*

[3] *$135,000 to < $155,000*

[4] *$75,000 to < $95,000*

[5] *$155,000 to < $255,000*

[6] *$455,000 to < $555,000*

6.88 With regards to specific issues raised in the evaluation, the PSCR stated that:

- The negative (or greater than 100%) transition probabilities observed result directly from the variability of the observed data with the week 26 and 52 results being slightly lower than those 4 weeks earlier, or later and argued such real-world data variability is not unexpected because clinical response varies over time and therefore does not impact the face validity of the model.
- The PSCR argued the sensitivity analyses using implausible response rates was not relevant or informative.
- A formulaic error was identified in the viral load transitions worksheet, which when amended accounts for instances where suppression occurs beyond the first cycle, which reduces the base case ICER to $75,000 to < $95,000 per QALY.

The formulaic error corrected viral load transitions based on clinical trial data, and did not affect the alternative base case presented in the evaluation, which applied modelled data from the initiation of the model.

6.89 The ESC considered the economic model presented in the resubmission was unreliable for decision-making. In providing this advice, the ESC considered that there were a number of key issues that resulted in the model producing counter-intuitive and often unrealistic and impossible inputs and outcomes, resulting in the model lacking both face validity and technical operability. The issues include:

- The use of observed data from the CAPELLA trial up to week 104. Whilst acknowledging it is generally preferable to use observed data when available, the ESC noted this input change resulted in transition probabilities to the < 50 copies/mL state of over 100%, as well as to the ≥ 200 copies/mL state of less than 0%, for both the LEN + OBR and OBR alone arms at certain time points (paragraph 6.74). The ESC did not accept the argument in the PSCR that this does not impact the face validity of the model (paragraph 6.88) and considered the fact that the use of observed data out to week 104 in the model led to mathematically impossible transition probabilities indicated the model lacks reliable technical operability and validity.
- The ESC also considered a decrease in the incremental benefit of LEN + OBR over OBR alone (RR = 2.8 versus 3.8 in the November 2022 submission[1]) leading to an increase to the incremental QALYs gain (3.09 versus 1.97 QALYs gained in the November 2022 submission) and a reduced base case ICER ($75,000 to < $95,000 per QALY versus $75,000 to < $95,000 per QALY in the November 2022 submission) compared with the November 2022 submission was inconsistent with the lower treatment effect. The ESC considered that given there was a substantially greater decrease in incremental benefit (27% lower) relative to the price decrease (around % lower), a higher ICER (with reduced QALYs gained) compared to the previous submission was expected (paragraph 6.73).
- Changes in the LEN + OBR virologic response in the model also led to disproportionate changes to OBR alone inputs, which led to additional unexpected and unreliable model behaviour, exemplified by how the model behaves in cycle 1, where an improvement in LEN + OBR efficacy led to an increase to the ICER (also discussed in paragraph 6.71).
- While the full Cohort 1 and 2 data from CAPELLA was used to inform the model and LEN effectiveness estimates, the ESC remained concerned the limited amount of patient data (n=72, compared to 24 in the November 2022 submission) was inadequate to inform a 16 health state economic model. The Pre-PBAC Response argued that all available data was used to inform the economic model, including updates out to 2 years of LEN trial data.

6.90 The Pre-PBAC Response argued the changes to the model made in the resubmission were reasonable and consistent with the previously expressed views of the PBAC and with the PBAC Guidelines, particularly the change to use data from the CAPELLA trial out to week 104.

[1] RR of 3.828 based on Cohort 1A vs OBR base case in Table 7, pg. 21 of the lenacapavir November 2022 PSD.

Drug cost/patient/year

Table 17: Drug cost per patient for LEN and OBR.

	Clinical evidence		Economics		Financial estimates [a]
	LEN + OBR	OBR	LEN + OBR	OBR	LEN
Initiation					
600mg orally day 1 and 2 ($)		-		-	[redacted][1]
Maintenance					
Cost/ injection ($)		-		-	[redacted][2]
Number of injections / year	2	-	2	-	2
Lenacapavir costs/ year ($)		-		-	[redacted][3]
OBR cost/ 3 months [b] ($)	$4,177.96	$4,177.96	$4,177.96	$4,177.96	Not explicitly estimated [c]
OBR costs/ year ($)	$16,711.85	$16,711.85	$16,711.85	$16,711.85	
Cost/patient/year (maintenance) ($)	[redacted]	**$16,711.85**	[redacted]	**$16,711.85**	**- [c]**

Source: 'Drug Acquisition costs' worksheet of attached economic model.
OBR = optimised background regimen
[a] The resubmission has included costs of additional OBR due to longer expected time alive (and thus treated with OBR). This is based on the estimated cost of $16,711.85 of OBR estimated in the economic section. However, this does not apply to costing of OBR costs in all patients in the financial estimates and only applies to a segment of an any individual patients total time on OBR treatment. Consequently, this has not been included in the comparison table.
[b] OBR costs are a weighted average of 3-month costs of individual components based on use in the CAPELLA trial with an adjustment to remove non-PBS-listed regimens.
[c] Not estimable as OBR costs were not explicitly estimated in financial estimates and only estimated incremental OBR costs were presented
The redacted values correspond to the following ranges:
[1] $0 to < $10 million
[2] $20 million to < $30 million
[3] $40 million to < $50 million

6.91 The total cost of LEN + OBR for one year of maintenance treatment was $ [redacted] based on an effective DPMQ of $ [redacted] for LEN and two injections per year (requested effective AEMP of $ [redacted] per injection set and a maximum quantity of 2), and total one-year costs of OBR of $16,712 based on a weighted basket of OBR costs based on CAPELLA OBR use. This compared to a cost of $16,712 for OBR alone.

6.92 These estimates differed from the previous submission, which estimated a total cost of LEN + OBR for one year of maintenance treatment as $ [redacted] based on an effective DPMQ of $ [redacted] for LEN and two injections per year, and total one-year costs of OBR of $18,670 based on a weighted basket of OBR costs based on CAPELLA OBR use. This compared to a cost of $18,670 for OBR alone.

6.93 As discussed in paragraph 3.3, the cost per tablet was updated in the resubmission, such that the total cost per course of oral tablets in the resubmission ($ [redacted] for five tablets) was less than the cost per course of oral tablets in the previous submission ($ [redacted] for four tablets).

6.94 The resubmission included costs of additional OBR in patients treated with LEN due to longer expected time alive. However, this was estimated by applying an assumed 22% longer life expectancy and based on the estimated cost of $16,712 of OBR estimated in the economic section rather than explicitly modelling the cost from OBR use per patient. Consequently, this has not been included in the comparison table.

Estimated PBS usage & financial implications

6.95 This submission was not considered by DUSC. As in the previous submission, the resubmission took an epidemiological approach to estimating use.

6.96 Table 18 presents a comparison of the data sources in the previous submission and the resubmission.

Table 18: Data sources and parameter values applied in the utilisation and financial estimates

Parameter/Assumption	Previous Submission (November 2022)		Current Submission (November 2023)	
	Estimate	Source	Estimate	Source
Prevalence number of HIV Patients	32,000	Kirby Institute (King, 2021)	30,000	Kirby Institute (King, 2021)
Percentage in care	96%	Kirby Institute (King, 2021)	91%	Kirby Institute (King, 2021)
Percentage on ART	91%		91%	
Percentage that are hMDR	0.84%	Bajema 2020	0.84%	Bajema 2020
Overall eligibility rate	0.73%	Calculated (0.96 x 0.91 x 0.0084)	0.70%	Calculated (0.91 x 0.91 x 0.0084)
Percentage of patients electing treatment (Years 1-6)	[redacted]	Sponsor estimate	[redacted]	Sponsor estimate
Total Number of hMDR PLWH to be treated with LEN by year 6	[redacted][1]	Calculated	[redacted][1]	Calculated
Effective price (AEMP) per oral tablet	$[redacted]	Sponsor	$[redacted]	Sponsor
Effective price (AEMP) per injection	$[redacted]	Sponsor	$[redacted]	Sponsor
Dosing	4 tablets initially (days 1-2), 1 injection every 6 months.	Draft PI	5 tablets initially (days 1-8), 1 injection every 6 months.	TGA PI
Co-pay	$15.72	Derived from darunavir 600mg (2021)	$12.05	Derived from darunavir 600mg (2022)
MBS increased use (#116)	NI	-	$81.05	Table 16, LEN PBAC PSD Nov. 2022
Increased use in OBR due to greater life expectancy	NI	-	$16,712 p.a. for up to an additional 22.6% of patients assumed to still be alive at 6 years, with an average of 14% annually.	Likely overestimated due to the modelling issues in the economic evaluation.

Blue shaded cells indicate values previously considered by the PBAC
Source: Table 4-1, p171 of the resubmission
ART = antiretroviral; HIV = human immune deficiency virus; hMDR = highly multidrug resistant; LEN = lenacapavir; MBS = Medicare Benefits Schedule; NI = not included; OBR = optimised background regimen; PI = product information; PLWH = people living with HIV; TGA = Therapeutic Goods Administration
The redacted values correspond to the following ranges:
[1] *< 500*

6.97 The PBAC and DUSC previously determined that using the literature derived estimate of 0.84% of PLWH being hMDR sourced from an analysis by the Kirby Institute (Bajema 2020) was likely to be reasonable. However, the PBAC considered the uptake in practice was highly uncertain, as it was unclear how many hMDR patients are realising a clinical benefit on their current regimen, (i.e., even if not fully virologically suppressed, but have stable viral load and/or CD4 cell counts) and whether patients and prescribers in this group would seek to switch patients to a LEN based regimen (paragraph 7.9, lenacapavir PSD, Nov 2022 PBAC meeting). The previous evaluation noted that even small differences in this input could have a substantial impact on financial estimates (paragraph 6.102, lenacapavir PSD, Nov 2022 PBAC meeting).

6.98 The resubmission stated that an Australian survey of clinical experts confirmed that 0.84% was a reasonable estimate and further stated the survey of 10 clinicians experienced in the treatment of PLWH, including hMDR, estimated that their practices were treating 46 hMDR PLWH (of the 1,665 PLWH in their care) who would meet the treatment criteria as proposed in the PBS restriction for LEN in this resubmission. The resubmission claimed that this therefore supported the estimate of < 500 hMDR PLWH in Australia in 2024 who would be eligible for LEN based on the requested restriction. It was unclear to what extent these 10 clinicians' practices would be representative of the average in Australia. However, of the 10 surveyed clinicians, seven reported a proportion of hMDR PLWH greater than 0.84% under their care, and the proportion of hMDR PLWH treated by the clinicians surveyed was 2.76% (46/1,665), which was three times that of the resubmission's assumption. The PSCR reiterated the estimate of the Australian hMDR population of 0.84% of PLWH was consistent with previous advice from DUSC and PBAC. Overall, the ESC considered the previous submission estimate of 0.84% of the PLWH population meeting the hMDR eligibility criteria for the proposed restriction remained likely to be the most reasonable estimate.

6.99 The number of eligible patients in year 1 in the resubmission (< 500) was lower than in the previous submission (< 500). This was due to a combination of a lower PLWH estimate and changes around assumption of proportion in care.

6.100 The resubmission applied the same uptake rate as the previous submission and anticipated that initially [redacted]% of eligible patients will be prescribed LEN (Year 1) and this is expected to peak at [redacted]% of the total eligible patient pool by year 3 of the listing before slightly declining ([redacted]%) due to an assumed diminishing proportion of patients initiating treatment over time. The resubmission noted that the commentary to the previous submission had suggested this uptake rate may be an underestimate, but the resubmission argued that as noted by the Australian survey of clinicians, a portion of hMDR PLWH have behavioural characteristics (i.e., some have particularly chaotic lives potentially with underlying mental health issues) which limit their adherence to antiretroviral therapy. Consequently, not all would opt to use LEN. This was likely unreasonable, as adherence (or lack thereof) implies that treatment was initiated in the first place, and lower uptake assumes that treatment is not initiated. Additionally, patients not initiating ARVs have already been factored into the estimates. The DUSC

previously considered that as LEN is a salvage and/or end of life therapy, most patients would want to access therapy (p5, lenacapavir DUSC advice, November 2022 PBAC meeting). The PBAC had considered that the uptake in practice was highly uncertain (paragraph 7.9, lenacapavir PSD, November 2022 PBAC meeting).

6.101 The ESC remained concerned that uptake was highly uncertain because the proposed positioning, as a new therapeutic option in the salvage/end of life setting was likely to make it an attractive option for some patients, whilst there may also be a reluctance to alter treatment regimens for other patients where an acceptable therapeutic outcome is being achieved through currently available (albeit highly individualised) combinations of ARVs. The ESC considered there was a risk of leakage to use in other PLWH who may not meet the strict definition of being hMDR in the proposed listing, however it was uncertain about the potential magnitude of that risk.

6.102 The resubmission incorporated additional OBR costs due to the improved life expectancy from LEN (as derived from the economic modelling). The mortality benefit was likely overestimated in the economic model (see paragraph 6.72). The resubmission estimated the incremental increase in OBR costs by applying a cost of OBR (DPMQ $16,712 per annum) to 14% (the average of each yearly increment modelled up to year 6) of the estimated patient years on treatment in the attached financial model. Overall, accounting for increased use of OBR did not have a substantial impact on the financial estimates for listing LEN in the resubmission's financial estimates.

6.103 Table 19 presents the estimated use and financial implications.

Table 19: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Eligible patients	1	1	1	1	1	1
Patients electing treatment	%	%	%	%	%	%
Number of patients treated (initiating and continuing)	1	1	1	1	1	1
Number of scripts dispensed [a]	1	1	1	1	1	1
Estimated financial implications of lenacapavir						
Cost to PBS/RPBS less co-payments	2	2	2	2	2	3
Estimated financial implications for additional OBR from life extension						
Cost to PBS/RPBS less co-payments	2	2	2	2	2	2
Net financial implications						
Net cost to PBS/RPBS	2	2	2	3	3	3
Net cost to MBS	2	2	2	2	2	2
Net cost to PBS/RPBS and MBS	2	2	2	3	3	3
Previous submission November 2022						
Net cost to PBS/RPBS	2	3	3	3	3	3

Source: Table 4-4, p175, Table 4-5, 4-6 p177, Source: Table 4-7, p178, Table 4-11, p182, Table 4-13, p182 of the resubmission.
Blue shaded cells indicate values previously considered by the PBAC
[a] Assuming 1 script per year for initiating tablets, 1 script per year for initiating injection and two scripts per year for maintenance as estimated by the resubmission.
The redacted values correspond to the following ranges:

[1] < 500
[2] $0 to < $10 million
[3] $10 million to < $20 million

6.104 The submission estimated a total net cost to government of $0 to < $10 million in Year 1, increasing to $10 million to < $20 million in Year 6, and a total of $50 million to < $60 million over the first 6 years of listing.

Quality Use of Medicines

6.105 The resubmission noted that a TGA compliant risk management plan (RMP) will be implemented and agreed through the registration process.

6.106 The resubmission noted that the EU RMP states that it is desirable to collect additional long-term safety information and data on safety in pregnancy and lactation, in addition to conducting routine post-marketing pharmacovigilance. Additional safety information will come from extended safety data from ongoing clinical trials in PLWH and an ARV pregnancy registry.

6.107 The resubmission also stated that the launch of LEN will be underpinned by comprehensive training of health care professionals on injection procedures. Instructions on injection procedures, including video or face-to-face injection training by third party registered nurses is expected to be provided. Demonstration injection kits along with training material will be provided to clinics.

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

Financial Management – Risk Sharing Arrangements

6.108 The resubmission did not propose a risk sharing arrangement.

7 PBAC Outcome

7.1 The PBAC recommended the Section 100, Highly Specialised Drugs Program (Community Access), Authority Required (STREAMLINED) listing of lenacapavir (LEN), in combination with optimised background regimen (OBR), for the treatment of patients with highly multi-drug resistant (hMDR) human immunodeficiency virus (HIV) infection. In making this recommendation, the PBAC accepted there is a clinical need for new and effective therapies for the treatment of people living with HIV that have few remaining effective treatment options, and that LEN as add-on therapy to OBR is effective for some patients in terms of achieving viral suppression. The PBAC considered LEN would be cost effective with a price reduction to achieve an incremental cost-effectiveness ratio (ICER) in the range of $45,000−75,000 per QALY using the alternative base case economic evaluation as presented in the evaluation. Noting there is likely to be a reluctance to alter treatment regimens for patients with hMRD HIV infection where an acceptable therapeutic outcome is being achieved through currently available combinations of anti-retrovirals (ARVs), the PBAC considered the uptake of LEN in the resubmission was overestimated. The PBAC considered there was a risk of leakage to people who do not meet the strict definition

of hMDR as per the proposed listing, and that this risk should be managed with a Risk Sharing Arrangement.

7.2 The PBAC was satisfied that LEN (as add-on therapy to OBR) provides, for some patients, a significant improvement in efficacy over OBR alone in people with hMDR HIV infection.

7.3 The PBAC recalled in its original consideration of LEN in November 2022 that it noted the level of engagement with care and treatment for people living with HIV was one of Australia's positive public health successes, and the number of patients meeting the definition of hMDR HIV infection was likely to be small. The PBAC reaffirmed this view and considered that while some hMDR patients may be adequately managed on individualised ART regimens, there was also a cohort of patients who are not adequately managed with current treatment options and/or experience substantial issues with their current treatments and would benefit from the availability of an additional treatment option which would increase their chances of achieving and/or maintaining viral suppression.

7.4 The PBAC recalled in its consideration of LEN in November 2022 that a simpler restriction, like that of maraviroc, would be more practical as it frames the number of past treatments in an affirmative manner rather than a deductive one. The PBAC considered a clinical criterion stating that a 'patient must have known multi-drug resistant HIV-1 infection to the main ARV drug classes, and require this treatment to construct a suppressive anti-viral regimen' was less complex than the current restriction and would simplify the process for prescriber's to identify an hMDR patient. The PBAC accepted the resubmission's proposal to re-specify the definition of virologic failure to a viral load greater than 200 copies per mL on two consecutive occasions, consistent with updated Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) guidelines. The PBAC considered this definitional change should be flowed on to existing PBS listed ARTs which have a similar restriction.

7.5 The PBAC reaffirmed its view expressed in November 2022 that the nominated comparator of OBR, as a basket of therapies and regimens which may be used in the hMDR population, was reasonable and reiterated that the composition of the OBR comparator should reflect contemporary Australian practice. The PBAC noted that fostemsavir and ibalizumab, agents not routinely used in Australia, were included in the basket and therefore, considered the composition of the OBR basket added uncertainty to the estimate of the magnitude of benefit with LEN over existing treatment options.

7.6 The PBAC noted, as for the November 2022 submission, the clinical claim was based on an unanchored indirect comparison between LEN + OBR and OBR alone. The estimated efficacy of LEN + OBR was from the CAPELLA trial (N= 72) with additional follow-up out to 104 weeks available in the resubmission (52 weeks in the original submission). The PBAC noted the comparison with OBR alone continued to be based on data out to weeks 48 (OBR) and 52 (LEN). The estimated efficacy for OBR alone was

from a meta-analysis of seven trials. Five of the trials were included in the November 2022 submission (BENCHMRK 1 & 2 (n= 118 and n=119, respectively), MOTIVATE 1 & 2 (n=118 and n=91, respectively) and VICTOR-E (n= 35)).

7.7 The two additional trials were BRIGHTE assessing fostemsavir and OBR (n=371) and TMB-301 assessing ibalizumab and OBR (n=40). The PBAC noted the percent of patients achieving viral suppression (HIV-1 RNA < 50 copies/mL) was higher in the BRIGHTE (49.6%) and TMB-301 (42.5%) studies than in the five studies included in the November 2022 submission (14.3% to 34.5%). The PBAC also noted a lower estimate of the percent of patients achieving viral suppression was used for LEN + OBR based on the combined data from CAPELLA Cohorts 1 and 2 (79.2%) rather than the data from Cohort 1 (83.3%). The PBAC noted that as a result, the estimated relative risk of viral suppression was reduced from 3.828 (95% CI: 2.592, 5.655) in the previous submission to 2.807 (95% CI: 1.928, 4.088) in the resubmission. Although more conservative, the PBAC considered the revised estimate remained uncertain due to being based on an unanchored indirect comparison with meaningful differences across the study populations, small patient numbers in CAPELLA, limitations with the applicability of the evidence to the proposed PBS population and variability in the viral suppression rates reported across the OBR studies. The PBAC further noted the resubmission's estimate of the proportion of patients achieving viral suppression when treated with OBR alone (29.3%) seemed low when compared with that estimated by 10 Australian clinicians surveyed by the sponsor (49.9-62.3%).

7.8 The PBAC noted the single arm data for LEN + OBR out to 104 weeks reported high and generally well-sustained rates of virologic suppression, with 77.8% of combined cohort 1 & 2 maintaining suppression at week 52, and 62.0% at week 104 which demonstrated LEN in combination with OBR is effective for the treatment of hMDR HIV infection.

7.9 The PBAC considered that based on the available data, the claim that LEN (in combination with OBR), is of superior comparative effectiveness to OBR alone was supported, in the proposed small population of patients with hMDR HIV infection. However, the PBAC considered the uncertainties in the clinical comparison meant that the magnitude of benefit could not be accurately determined.

7.10 The PBAC noted updated safety data out to week 104 was presented in the resubmission, which found a similar safety profile of LEN over this longer period and did not identify any new safety signals. While noting the data was limited due to the small size of the trial, the PBAC reaffirmed its view from November 2022 that the claim of non-inferior comparative safety to OBR alone was overall likely to be reasonable.

7.11 The PBAC noted the ESC advice that the economic model in the resubmission was unreliable for decision making for the reasons outlined in paragraph 6.89. The PBAC considered the key model uncertainties reflected the limited clinical evidence available for the small population with hMDR HIV infection. The PBAC noted a more conservative estimate of the efficacy of LEN was assumed in the resubmission model

compared with the November 2022 model (paragraph 7.6) and considered this was appropriate, although noted the estimate remained uncertain. The PBAC noted the approach of using observed rather than modelled data for the first 104 weeks of the model was inconsistent with the approach used in the November 2022 submission and was not conservative. The PBAC considered the alternative base case presented in the evaluation, in which modelled data is applied from model initiation, to be more appropriate noting the small amount of data to inform each transition. The PBAC noted that the alternative base case resulted in more conservative estimates of viral suppression for the OBR arm and that it was unaffected by the formulaic error noted in the PSCR. The PBAC noted the ICER for the alternative base case was $115,000 to < $135,000 per QALY. The PBAC considered based on the extent of the model uncertainties, consistency with its previous recommendations for maraviroc[2] and darunavir[3] for drug resistant HIV, and in the context that LEN provides a further salvage regimen for the hMDR population, that LEN would be considered cost-effective with a price reduction that resulted in an ICER in the range of $45,000−75,000 per QALY. The PBAC further considered this resulted in a price for LEN that was reasonable in the context of the accepted cost-effective prices for maraviroc and darunavir, and therefore that this frame of reference alleviated remaining concerns it had about the reliability of the LEN economic model.

7.12 The PBAC noted the underlying assumption that 0.84% of the Australian population of people living with HIV (PLWH) being hMDR (based on an analysis by the Kirby Institute) was unchanged from the previous submission and remained reasonable. The PBAC considered the revised assumptions around the prevalence of PLWH (reduced from 32,000 to 30,000 in year 1) and proportion in care (reduced from 96% to 91%) to be reasonable and noted the net result of these changes reduced the estimated number of eligible patients in Year 1 from < 500 to < 500. Overall, the PBAC considered the estimate of approximately < 500 eligible hMDR patients, as presented in Table 19, was likely to be reasonable.

7.13 The PBAC considered the uptake of LEN to be uncertain noting that as a new therapeutic option in the salvage setting it was likely to be an attractive option for some patients, whilst there would also be a reluctance to alter treatment regimens for other patients where an acceptable therapeutic outcome is being achieved through currently available (albeit highly individualised) combinations of ARVs. In the context of the Australian clinician survey reporting that OBR is considered to be effective for 50−62% of the hMDR population, the PBAC considered that in practice, the uptake of LEN was likely to be less than % in year 1, and that uptake of 50% would be more reasonable. The PBAC considered the uptake assumed in the resubmission for the subsequent years (% decreasing to %, Table 19) to be reasonable.

[2] https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2009-11/pbac-psd-Maraviroc-nov09
[3] https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2007-07/pbac-psd-darunavir-ethanolate-july07

7.14 The PBAC considered there was a risk of leakage to use in PLWH who do not meet the strict definition of hMDR as per the proposed listing, and that this risk should be managed with a Risk Sharing Arrangement (RSA). The PBAC considered the financial caps for the RSA should be based on the revised estimates as outlined in paragraph 7.13 and the rebate for use above the caps should be high given the use of LEN is likely to not be cost-effective in this population.

7.15 The PBAC advised that LEN should not be treated as interchangeable on an individual patient basis with any other drugs.

7.16 The PBAC advised that LEN is suitable for prescribing by nurse practitioners.

7.17 The PBAC recommended that the Early Supply Rule should apply.

7.18 The PBAC noted the flow-on restriction changes to amend the definition of virologic failure from greater than 400 copies per mL to greater than 200 copies per mL for applicable PBS listings – maraviroc, etravirine, darunavir and the combination drugs darunavir + cobicistat and darunavir + cobicistat + emtricitabine + tenofovir alafenamide.

7.19 The PBAC noted the resubmission claimed that the 'Rule of Rescue' would apply to individuals who have no fully active ARV options available to construct a viable ARV regimen. The PBAC did not accept this claim noting that for the majority of patients alternative pharmacological interventions are available in the form of highly individualised ART regimens and, although the magnitude of the clinical improvement was unable to be reliably quantified, it was not considered to provide a rescue from the medical condition.

7.20 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 lenacapavir:

a) The improvement in clinical efficacy remains uncertain over alternative therapies, on the basis of the clinical evidence provided;

b) The treatment is not expected to address a high and urgent unmet clinical need many patients are currently adequately treated on highly individualised OBR regimens; 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.

7.21 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Proprietary Name and Manufacturer
LENACAPAVIR lenacapavir sodium 300 mg tablet, 5	NEW 1	1	5	0	Sunlenca®
LENACAPAVIR lenacapavir sodium 464 mg/1.5 mL injection, 2 x 1.5 mL vials	NEW 2	1	2	0	Sunlenca®

	Category / Program: Section 100 – Highly Specialised Drugs Program {Community Access}
	Prescriber type: ☒Medical Practitioners ☒Nurse practitioners
	Restriction Level / Method: ☒Authority Required (Streamlined) [code new 2B]
	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.
	Indication: Human immunodeficiency virus (HIV)
	Clinical criteria:
	Patient must have known multi-drug resistant HIV-1 infection to the main antiretroviral drug classes, and require this treatment to construct a suppressive anti-viral regimen.
	AND
	Clinical criteria:
	The treatment must be in addition to optimised background therapy.
	Prescribing Instructions: Virological failure is defined as a viral load greater than 200 copies per mL on two consecutive occasions, while clinical failure is linked to emerging signs and symptoms of progressing HIV infection or treatment-limiting toxicity.
	Prescribing Instructions: Genotypic resistance to individual anti-retroviral drugs is to be determined by genotypic testing.
	Administrative Advice: For the purposes of this restriction, the main antiretroviral classes include nucleotide/nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INTSIs) and protease inhibitors (PIs).

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

Flow-on restriction changes:

As per paragraph 7.18, amend the definition of virologic failure from greater than 400 copies per mL to greater than 200 copies per mL for applicable PBS listings – maraviroc, etravirine, darunavir and the combination drugs darunavir + cobicistat and darunavir + cobicistat + emtricitabine + tenofovir alafenamide.

- *"Virological failure is defined as a viral load greater than **400 copies** per mL on two consecutive occasions, while clinical failure is linked to emerging signs and symptoms of progressing HIV infection or treatment-limiting toxicity."*

- *New: "Virological failure is defined as a viral load greater than **200 copies** per mL on two consecutive occasions, while clinical failure is linked to emerging signs and symptoms of progressing HIV infection or treatment-limiting toxicity."*
- *Relevant PBS item codes:*
  10329P / darunavir 600 mg tablet, 60
  10367P / darunavir 800 mg tablet, 30
  10301E / etravirine 200 mg tablet, 60
  10318C / maraviroc 150 mg tablet, 60
  10355B / maraviroc 300 mg tablet, 60
  10903W / darunavir 800 mg + cobicistat 150 mg tablet, 30
  11955F / darunavir 800 mg + cobicistat 150 mg + emtricitabine 200 mg + tenofovir alafenamide 10 mg tablet, 30
  12111K / darunavir 800 mg tablet, 30
  12946J / darunavir 600 mg tablet, 2 x 30

9 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.

10 Sponsor's Comment

The sponsor had no comment.